HEMATURIA EVALUATION IN THE PRIMARY CARE SETTING

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DISCLOSURES

• None
QUESTION #1

• T/F. Your patient is seen for a routine visit and a UA is performed. He has microscopic hematuria with 1+ blood on the dipstick. You make a note that this will need further evaluation, but when he leaves the office, his labs return and his INR is 10.
• Because of this, you do not have to further evaluate this, as his hematuria may be easily explained by his supra therapeutic INR.

QUESTION #2

• T/F. Your patient comes to the office with a complaint of pinkish bloody urine that started this morning. She noted NO clots. The UA is heme positive 3+ and also protein 3+. The UA was negative for LE and nitrates. You should proceed with a work up for a NON-glomerular source as her heme positivity responsible for the proteinuria.

QUESTION #3

• T/F Your 48 yo pt works as a painter and is a smoker. He is found to have asymptomatic hematuria. There is no evidence for a glomerular source of bleeding (no proteinuria, creatinine is normal). His work-up including CT urography, urine cytology, urine culture, and cystoscopy were negative. You should tell the patient that all is well and that no further follow-up is needed (according to the AUA guidelines).
INTRODUCTION

• Asymptomatic hematuria prevalence of <1%-16%
• 25% MACROSCOPIC hematuria are due to urologic cancers and 34% due to other significant urologic dz.
• 1-10% MICROSCOPIC hematuria due to urologic cancers.
• 40% of the time, no cause is found for asymptomatic microscopic hematuria

MACROSCOPIC vs MICROSCOPIC

– In pts > 50 yoa who have GROSS hematuria + one risk factor (male, smoking, > 25 rbc/ hpf) the prevalence of urinary tract CA 11%. Versus patients < 50 yoa with microscopic hematuria the prevalence was 0.2% (Liu RK, Lahannan RP, et al. Stratifying risk of urologic malignancy tumors in patients with asymptomatic microscopic hematuria. May Clin Proc 2013; 88:129)

– In another study, 1930 pts were followed in a hematuria clinic. 12% had bladder CA, 0.7% had kidney and upper tract tumors. 61% had no cause found (Khadra MH, Pickard RS et al. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol 2000; 163:524)

50-59 males yoa group: Gross hematuria 20% malignancy
Microscopic 1.9% malignancy

60-69 males yoa group: Gross hematuria 29% malignancy
Microscopic 8% malignancy

So, what is the worst case scenario?

• Incidence of Kidney and renal pelvis cancer
  – Estimated new cases 2015 about 61,500
  16 / 100,000
  – 4% of all cancer cases
  – 14,000 deaths
  – Survival @ 5 years (2005-2011 stats) 73%
  – 90% bladder CA presents as hematuria

• Incidence of GN –
  – 7 cases per 1,000,000 patients

• Incidence of some glomerular disorder 0.5-1% of the population.
INTRODUCTION

• Screening for hematuria with urinalysis in patients with no symptoms to suggest pathology is **NOT RECOMMENDED**

• However there are some pts in whom routine UA should be done (even with lack of obvious clinical symptoms):
  - H/O DM, CVD, HTN, HLD, obesity, metabolic syndrome, smoking, HIV or HCV, SLE, CA
  - Family history of kidney disease
  - Sickle cell trait
  - Treatment with potentially nephrotoxic drugs
  - ALL pts > 60 yoa (KDIGO although this has not been widely accepted)

Starting the evaluation

DIPSTICK -- HEMATURIA

• Dipsticks detect 1-2 RBC / hpf
  - 1+ blood. Sensitivity 91-100%. Specificity 65-99%
INITIAL EVALUATION

1. Is the hematuria gross or microscopic?
   - Real blood or false positive for blood
2. Is the hematuria transient or persistent?
3. What is the surrounding history / associated symptoms
4. What are the patient characteristics (sex, age, occupation, medical history). Is there any significant family history
5. Glomerular or non-glomerular

#1 GROSS or MICROSCOPIC

- Macroscopic hematuria (gross hematuria)
- Microscopic hematuria:
  - AUA guidelines 3 RBC/hpf in a spun urine specimen reviewed under the microscope on 2 of 3 properly obtained urine specimens

#1 GROSS or MICROSCOPIC

- Centrifuge the urine to see if the red/brown color is the urine sediment or the supernatant ALSO to see if RBC in sediment
  - If supernatant is CLEAR (and the supernatant UA heme -ive) with sediment that has 3 RBC/hpf then it is HEMATURIA
- Exception of this would be in the case of pt with gross hematuria and a very dilute urine (< 1.007). The lysis of RBC in dilute urine would produce a red supernatant
RED/BROWN URINE – IS IT BLOOD??? (cont)
• If the supernatant is RED/BROWN:
  – And check of the supernatant is heme +ive with sediment negative for RBC:
    • Metabolites: Porphyria (porphyrin), bile, melanin
    • Medications: phenaopyridine, chloroquine, ibuprofen, nitrofurantoin, phenolphthalein, rifampin, defuroxamine, doxorubicin, iron sorbitol
    • Foods: beets, blackberries
  – And check of supernatant is heme +ive and the sediment is negative for RBC:
    • Myoglobinuria
    • Hemoglobinuria

FALSE POSITIVES – positive dipstick in the ABSENCE of blood cells in urine sediment
• Myoglobinuria
• Hemoglobinuria
• Concentrated urine
• Semen

“FALSE POSITIVE” – positive dipstick AND presence of blood on urine sediment BUT due to non-pathologic causes
• Contamination of urine from menstrual blood
• Rigorous exercise
FALSE NEGATIVE on urine dipstick

- Capoten
- Increased specific gravity
- pH < 5.1
- Proteinuria
- Vitamin C – urine ascorbic acid can interfere with peroxidase rxn

#2 TRANSIENT or PERSISTENT

- Inquire about any recent vigorous exercise
- Menstruation
- REPEAT an abnormal urinalysis in a few days to see if transient or persistent

- ? UTI

- There is NO cause of low level hematuria (without other concerning signs and symptoms) requires immediate diagnosis
#3 SURROUNDING HX / ASSOCIATED SYMPTOMS

• “locating the lesion”
  – Timing of hematuria:
    • Start of urination – problem with distal urethra
    • End of urination – problem with bladder neck, posterior urethra or prostatic urethra
    • Throughout urination – problem with upper urinary tract or upper bladder source
  – Color of urine:
    • Cola-colored – glomerular
    • Pink or red – renal pelvis and lower urinary tract

SURROUNDING HX / ASSOCIATED SYMPTOMS (con’t)

• Pyuria and dysuria:
  – indicate UTI but can also be seen in bladder CA

• Pain of lack of pain:
  – CVA – pyelonephritis
  – Dysuria UTI
  – Colicky flank pain associated with nausea, vomiting suggests nephrolithiasis
  – Flank pain may also be seen in CA or loin-pain hematuria syndrome
  – Painless – CA (especially with gross hematuria)

SURROUNDING HX / ASSOCIATED SYMPTOMS (cont)

• Edema and/or oliguria:
  – RPGN

• Any constitutional symptoms (fever, arthritis, myalgia, rash, weight loss, night sweats):
  – RPGN
• Hemoptysis
SURROUNDING HX / ASSOCIATED SYMPTOMS (cont)

- Prostate issues?
  - BPH is associated with increased vascularity and the new vessels can be fragile
  - BUT the presence of BPH should not prevent further evaluation of hematuria. As older men are more likely to have more serious disorders such as CA of the prostate or bladder.
  - FINASTERIDE can suppress the hematuria

SURROUNDING HX / ASSOCIATED SYMPTOMS (cont)

- Any recent respiratory infection?
- Any prior episodes of hematuria?
- Any history of nephrolithiasis?
- Any history of radiation treatments?
- Sickle cell trait or disease?
- Travel or residence in areas endemic for schistosoma haematobium or TB?
- History of hepatitis or HIV?

#4 PATIENT CHARACTERISTICS -- medications

- Cyclophosphamide
- Analgesics
- Vitamin C
- Medications that can produce a red urine -- pyridium
- What about ASA and coumadin ??
Question # 1
What about coumadin / being supratherapeutic?

T/F. Your pt is seen for a routine visit and a UA is performed. He has microscopic hematuria with 1+ blood on dipstick. You make a note that this will need further evaluation, but when he leaves the office, his labs return and his INR is 10. Because of this, you do not have to further evaluate this, as his hematuria may be easily explained by his supratherapeutic INR.

Retropective study

Overall, a urinary tract tumor was dx in about 25% of pts, and other treatable pathologic findings were found in about 50% in the study group. A higher incidence of hemorrhagic cystitis occurred in the patients taking aspirin.

Patient characteristics

• Males > females for RCC
• AGE:
  – > 45 years of age with isolated hematuria – 20% will have abnormality on urologic work-up, with half having malignancy
  – < 45 years of age with isolated hematuria – 2% will have significant urologic disease

Patient characteristics

• RACE:
  – African-American – sickle cell
  – Asian – consider IgA
• Smoking?
• Occupational history? Any exposure to dyes or chemicals?
PATIENT CHARACTERISTICS/RISK FACTORS of UROLOGIC CA (AUA)

- Male gender
- Age > 35
- Current or past smoking history
- Occupational dye exposure (benzenes or aromatic amines)
- History of gross hematuria/chronic cystitis
- Pelvic irradiation/cyclophosphamide
- Analgesic abuse
- Chronic indwelling foreign body

RCC risk factors

- Smoking
- Hypertension
- Occupational exposure to toxic compounds – cadmium, asbestos, petroleum.
- Obesity
- Acquired cystic disease of the kidney
- Analgesic abuse nephrology
- Genetic predisposition.

FAMILY HISTORY

- Alport’s – deafness and renal failure
- Benign familial hematuria – other members of the family with hematuria
- Sickle cell syndromes – unexplained hematuria with ethnic origins from Africa, the Middle East and Mediterranean countries
- PCKD
- FAMILIAL syndromes for RCC


# 5 Glomerular vs extraglomerular

**Extra glomerular**
- If MACROSCOPIC – red or pink color
- Clots – may be present
- Proteinuria < 500 mg/dL
- RBC morphology normal
- RBC casts – NOT present

**Glomerular**
- If MACROSCOPIC – red, smoky brown or “coca-cola”
- Clots – NOT present
- Proteinuria > 500 mg/dL
- RBC morphology – dysmorphic
- RBC casts – may be present
- From immune-mediated injury or non-immune like TBM

**WORK-UP**

- If there is gross hematuria, **SEND TO UROLOGY regardless of risk factors and age…….**
- If there are NO concerning risk factors AND there is a suspicion for a transient process, RECHECK UA in a few weeks
  - Specifically if UTI, RECHECK in 6 weeks (after the pt is treated).
CHECK RENAL FUNCTION

- Any proteinuria?
  - > = 500 mg/dL

- Any elevation in creatinine from baseline?

**Question #2 Dipstick proteinuria**

T/F: Your pt comes to the office with a c/o pinkish-bloody urine that started in the AM. She noted some clots. On the UA she is heme 3+ and also 3+ proteinuria. The UA is neg for LE and nitrates.

- You should proceed with a work up for a NON-glomerular source as some degree of her heme +ive is contributing to the proteinuria.

- Hematuria alone does not typically lead to a significant increase in protein excretion.

- A dipstick test for protein that is > 1+ is RARELY observed with non-glomerular bleeding even with gross hematuria UNLESS the gross hematuria is VERY LARGE.
CT urography (AUA guideline)

- Should be performed in ALL pt with unexplained persistent hematuria if no renal insufficiency, contrast allergy, pregnancy
  - Those without infection, glomerular hematuria or other known source of hematuria
- Should be performed in ALL patient with transient hematuria who have risk factors for malignancy. If no renal insufficiency, contrast allergy, or pregnancy

CT scan with and without contrast

- Evaluation of the upper tract
- Imaging of choice
US with retrograde pyelogram, MRI or MR urography, Non-contrast CT

- Renal insufficiency
- Contrast allergy
- Pregnancy
- LOW RISK MALIGNANCY

Cystoscopy

- Should be done in ALL patient with GROSS hematuria (unless active UTI, stones):
- Should be done in ALL with persistent MICROSCOPIC hematuria if it is not explained (otherwise negative work-up) and there are risk factors (irritative voiding symptoms, smoking, chemical exposures).
- Generally not necessary for non-smokers < 35

Urine cytology

- AUA guideline:
  - Urine cytology and urine markers are NOT recommended as part of the ROUTINE eval of asymptomatic microhematuria patient
  - Lacks sufficient clinical reliability to be used in the routine evaluation of asymptomatic hematuria
  - Sensitivity of 0-100%, Specificity 63-100%
  - BUT can be used IN CONJUNCTION in the HIGH risk patient or if persistent microhematuria with negative work up
- A-ive cytology does NOT PRECLUDE a full work up
**So what are we looking for?**

**DIFFERENTIAL DX of isolated hematuria**

- **Glomerular cause:**
  - Familial: Fabry dr, Alports, Nail-patella syndrome, TBM dr
  - Primary glomerulonephritis:
    - FSGS
    - Goodpasture syndrome (anti-GBM disease)
    - Henoch-schonlein purpura
    - IgA nephropathy
    - MPGN (mesangio proliferative glomerulonephritis)
    - Post- infectious GN
    - RPGN
  - Secondary glomerulonephritis:
    - Hemolytic uremic syndrome and TTP
    - SLE
    - Vasculitis

- **Metabolic causes/ renal causes:**
  - RENAL CELL CA
  - Pyelonephritis
  - PCKD
  - Malignant hypertension
  - Papillary necrosis
  - Renal vein thrombosis
  - Sickle cell disease or trait
  - AVM
  - Hypercalcuiuria
  - Hyperuricosuria
  - Loin-pain hematuria syndrome
  - Medullary sponge kidney
DIFFERENTIAL DIAGNOSIS
of isolated hematuria (cont)

- Non-renal
  - Nephrolithiasis
  - Ureteric CA
  - Bladder – CA, cystitis
    - schistosoma haematobium
    - TB infection
  - Prostate – BPH, prostatitis, CA
  - Ureteral lesions

INTERMISSION

Suspecting GLOMERULAR BLEEDING

- NO CLOTS
- red, smoky brown or “coca-cola”
- Proteinuria > 500 mg/d
- RBC morphology – dysmorphic
- RBC casts – may be present
- From immune-mediated injury or non-immune like TBM
DYSMORPHIC RBC

RBC CAST

IgA nephropathy

- Can see Gross hematuria especially < 5 days after a bacterial or viral URI (unlike post-streptococcal GN where hematuria is between 1-3 weeks with Grp A Strep pharyngitis and 3-6 weeks with Strep skin infection)
- Rare to see a family history
- Course can be indolent, but 1/3 reach ESRD after 20 years
Thin Basement membrane disease
• Rare to see gross hematuria (< 10% cases)
• May see a family history (Autosomal Dominant)
• Frequency in the general population as high as 5-9%
• NO renal failure
• Typically benign course

Alport’s syndrome (hereditary nephritis)
• Can see Gross hematuria (can also follow an upper respiratory infection at an interval of < 2 days)
• Family history of renal failure (esp males)
• Deafness present (sensorineural hearing loss)
• X-linked dominant inheritance and autosomal recessive forms
• 10% with X-linked Alport’s have de novo mutations

RPGN
• Clinically:
  – Edema
  – HTN
  – Gross hematuria/ microscopic hematuria
  – Proteinuria
  – GFR < 50% within months
  – Upper and/or lower respiratory tract involvement
• Constitutional symptoms:
  – Fever, myalgia, anorexia, weight loss, malaise, night sweats
RPGN (cont)
- In US 7 cases per 1,000,000 persons a year
- Caucasians > African –Americans 7:1
- Male to female 1:1
- Middle to 6th decade of life
- LABS:
  - C3, C4
  - ANCA (c-ANCA, p-ANCA, anti MPO, anti PR3)
  - ANA, ds-DNA
  - Cryoglobulins
  - Anti-GBM

CASE STUDIES

Ms. MS
- A 33- yo female with no significant medical history. She does not have any risk factors for urologic malignancy. She is here for a c/o dysuria and a UA is done
- UA with nitrates and 2+ blood. She has 1+ proteinuria. You send her for a urine culture and start her on CIPRO for 3 days and she gets better.
- What should you do next?
TRANSIENT HEMATURIA/ HEALTHY ASYMPTOMATIC HEMATURIA

- Also should be inquiring about exercise
- Need to confirm if the hematuria is persistent or transient and if it is due to a non-pathologic cause.
- She is < 35 with NO risk factors
- Hematuria is NOT gross.
- And she has a UTI
- REPEAT UA in 6 weeks (AUA guideline)

Case of transient hematuria: UTI exercise

Ms. SB

- Ms. SB is a 47 year old smoker (70 pack year smoker) who is presenting for a follow-up exam when her pet iguana bit her finger. The wound is well-healed with no redness, no infection. While she is there, she reports that she would like a full physical exam because she has noted some dysuria.
- You do UA in your office and she is HEME + with trace proteinuria. NO nitrites or leukocytes.
- Renal function is normal. What is next?
Malignancy work-up

- You have determined there is no transient cause of the hematuria and that her renal function is wnl.
- She is > 35 yoa with risk factor of:
  - Heavy smoking
- Upper tract imaging – CT urography
- Urology referral

Mr. AS

- Mr. AS is a 66 year old whom you tx for anxiety and paranoia.
- He presents with one episode of painless gross hematuria. He does not have an infection. You determine it is true hematuria. He does not have any risk factors. His creatinine of 1.2 mg/dL is stable. He does NOT have proteinuria on UA.
- There is no FMHx of kidney disease. He has never had this before. What do you do next?
**WORK UP FOR GROSS HEMATURIA**

- CT urography
- Urologic referral -- cystoscopy

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**Mr. CW**

- Mr. CW is a 34 yo who you saw one year ago. Other than obesity and a penchant for doughnuts, he has no PMHx.
- He presents to the office because he went to a wellness fair and had a UA that showed microscopic hematuria and “a lot” of proteinuria (he cannot remember how much). He denies any clots. He does not have any flank pains. He has noticed some “stuffiness” in his ears and he has been more fatigued. He has not been exercising and it is not a UTI.

- On exam BP 170/80, pulse of 76. Wt has decreased by 10 lbs and it was un-intentional.
- He has been more fatigued lately. He does not have a rash.
- He is started on treatment for an ear infection. What should be done next?

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**RPGN WORK UP**

- CHECK RENAL FUNCTION and if increased above the baseline, NEPHROLOGY REFERRAL

- Concern for RPGN:
  - Microscopic hematuria with proteinuria
  - No evidence this is transient
  - Some upper respiratory symptoms (ear stuffiness)
  - Constitutional symptoms of fatigue and weight loss

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“Evaluation of Microhematuria and Gross Hematuria in the Primary Care Setting”
Tina Y. Ko, D.O.

Mr. HIS

- Mr. HS is a 36 yo who presents for his routine physical for work. He is HEME positive on his UA.
- He works at a high stress job does not smoke. He does not have any occupational dye exposures or history of pelvic irradiation or cyclophosphamide exposure. He does not have risk factors.
- You confirm this is true hematuria on repeat testing and also by urine sediment analysis. His renal function is normal on serum creatinine evaluation and urine albumin check.
- You send him for an evaluation – CT urogram, cytology, and cystoscopy are negative.
- What do you do next?

IF ASYMPTOMATIC HEMATURIA AND WORK UP NEGATIVE … what then?

- T/F Your 48 year old patient who works as a painter and is a smoker is found to have asymptomatic hematuria. His work-up including CT urography, urine cytology, urine culture, cystoscopy were negative. There is no evidence that this is a glomerular source of bleeding. You assure the patient that all is well and that no further follow up is needed.

- FOLLOW-UP of pts with TRANSIENT hematuria:
  - If high risk for CA, ANNUAL UA. After 2 consecutive NEG UA, may stop follow-up.

- FOLLOW-up of pt with PERSISTENT hematuria:
  - If NOT high risk for CA, Annual UA and if persists for 3-5 years, repeating initial urologic w/u (CT urogram/cytology/cystoscopy).
  - If high risk for CA, consider repeat US and cystoscopy at one year.
PERSISTENT MICROSCOPIC HEMATURIA LONG TERM FOLLOW UP

- 1.2 million Jewish candidates (60%) male ages 16-25 were screened with dipstick and the dipstick hematuria was confirmed by microscopy. Present in 0.3% candidates.
- Normal GFR, no proteinuria, normal US. Seen by nephrologists.
- Increased ESRD rates on 20 year follow-up.
  - 34 vs 2 per 100,000 person years.
  - Hazard ratio of 18.5 (12.4-27.6)
- ESRD due to primary glomerular disease

Persistent Asymptomatic Isolated Microscopic Hematuria in Israeli Adolescents & Young Adults & Risk of ESRD. Vivante et al. JAMA. 306;7: 729

SUMMARY

- Is it gross or microscopic?
- Is the “hematuria” real?
- If it is real, then is it persistent or is it transient?
- What are the patient characteristics? / Is the person high risk for malignancy?
  - Age, Race
  - Risk factors (smoking, chemical exposures)
  - Associated symptoms (pain, edema, weight loss)
  - Family history
- Is the renal function normal and is there any proteinuria?

Dipstick testing positive for blood

- Microscopic urinalysis
- Positive
  - Assess for UTI and other causes (vigorous exercise, menstruation, recent urologic procedure)
  - Repeat UA 6 w after tx or after stop activity
- Negative – NO additional w/u
- Positive
  - RENAL FUNCTION TESTING (Cr, proteinuria)
  - Positive
  - Nephrology referral
  - ? RPGN, other GN
- Negative
  - Repeat UA 3 X @ 6 w intervals
  - Positive
  - Negative – NO additional w/u

Negative – NO additional w/u

Negative – next slide
Assess for:
- risk factors malignancy
- contraindications to radiation
- allergies to contrast
- Renal Insufficiency

LOW risk malignancy or RI or radiation sensitivity or contrast allergy

Low optimal imaging with MRI, urography, US, non-contrast CT, MRI, retrograde pyelography AND UROLOGIC referral

Cystoscopy

NEGATIVE
- ANNUAL UA for 2 years

NOTE: if no urological abnormality

POSITIVE
- Annual repeat UA +ive
- Repeat anatomic eval w/ 3-5 years

END