This document was last amended in October 2020 to reflect literature that was released since the original publication of this content in May 2012. This document will continue to be periodically updated to reflect the growing body of literature related to this topic.

HEMATURIA

KEY WORDS: Hematuria, Cystoscopy, Urothelial carcinoma, CT Urography

LEARNING OBJECTIVES:

At the end of undergraduate medical training, the learner will be able to:

1. Define microscopic hematuria
2. Describe the proper technique for performing microscopic urinalysis
3. Identify risk factors that increase the likelihood of diagnosing urologic malignancy during evaluation of hematuria
4. Discuss the evaluation of hematuria

DEFINITION

Hematuria is defined as the presence of red blood cells in the urine. When visible to the naked eye, it is termed gross hematuria. When detected by the microscopic examination of the urinary sediment, it is termed microscopic hematuria.

The dipstick method to detect hematuria depends on the ability of hemoglobin to oxidize a chromogen indicator with the degree of the indicator color change proportional to the degree of hematuria. Urine dipstick testing has a sensitivity of 95% and a specificity of 75% for detecting microscopic hematuria. False positive readings can be due to free hemoglobin (e.g. menstrual blood), myoglobin due to exercise, dehydration and certain antiseptic solutions (povidone- iodine). Knowing the serum myoglobin level and results of the microscopic urinalysis will help differentiate these confounders. Thus, positive dipstick results should be confirmed with microscopic evaluation. The presence of significant proteinuria (2+ or greater) suggests a nephrologic origin for hematuria. The presence of many epithelial cells suggests skin or vaginal contamination, and another sample should be collected.

Microscopic examination of urine is performed on 10 mL of a midstream, clean-catch specimen that has been centrifuged for 10 minutes at 2000 rpm or for 5 minutes at 3000 rpm. The sediment is re-suspended and examined under high power magnification. With this method, microscopic hematuria is defined as ≥3 red blood cells per high powered field (rbc/hpf) on a single specimen.

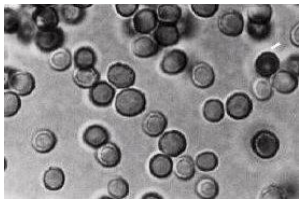

Figure 1. Red blood cells observed on high power microscopy of urine sediment.

The presence of red cell casts, dysmorphic red blood cells, leukocytes, bacteria and crystals should also be included in the urinalysis report.

EPIDEMIOLOGY

Hematuria is one of the most common urologic diagnoses accounting for 20% of urology consultations. The prevalence of microscopic hematuria ranges from 2-31% depending on the population studied. The likelihood of finding significant urologic oncologic disease varies with associated risk factors which include:

Table 1. Risk Factors for Malignancy in Patients with Hematuria

- Older age
- Male gender
- History of cigarette smoking
- History of occupational chemical benzene or aromatic amines exposure (e.g. dyes, rubber, petrochemicals)
- History of cyclosphosphamide/ifosfamide chemotherapy
- History of pelvic radiation
- Irritative voiding symptoms (urgency, frequency, dysuria)
- History of chronic indwelling catheters
- Family history of urothelial cancers

Even though the likelihood of documenting a urologic malignancy in patients referred for microscopic hematuria is less than 5%, no major health organization currently recommends routine screening for microhematuria in asymptomatic patients. Instead, the decision to obtain a urinalysis (dipstick or microscopic) is based on the interpretation of clinical findings by the evaluating physician.

ETIOLOGY

The source of red blood cells in the urine can be from anywhere in the urinary tract between the kidney glomerulus and the urethral meatus.

When considering the evaluation of hematuria, hematuria should be separated into glomerular or non-glomerular etiologies. Glomerular causes arise from the kidney itself. In general, glomerular hematuria is the purview of nephrologists, whereas urologists are concerned with structural and pathologic conditions that are visible on imaging and/or endoscopic examination. The presence of dysmorphic RBC, proteinuria, cellular casts, and/or renal insufficiency warrant concurrent nephrological and urologic evaluation.

Urinary findings suggestive of a glomerular source for the patient's hematuria include dysmorphic red blood cells (Figure 2), significant proteinuria, and red cell casts (Figure 3). The presence of red cell casts in the urinary sediment is strong evidence for glomerular hematuria.

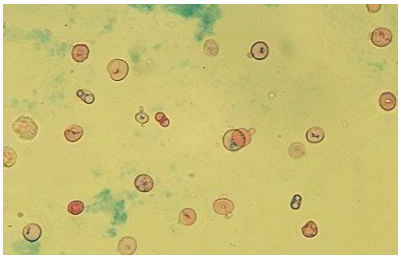

Figure 2. Example of dysmorphic red blood cells consistent with renal or glomerular hematuria.

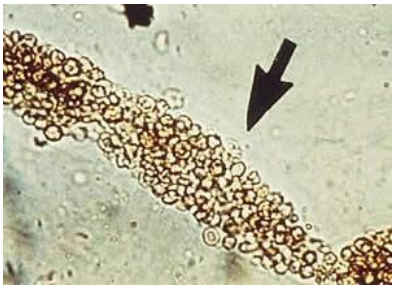

Figure 3. Example of a red cell cast (arrow) in the urinary sediment.

Although protein may enter the urine along with the red blood cells regardless of the origin of the hematuria, significant proteinuria (>1,000 mg/24 hours) likely indicates a renal parenchymal process and should prompt consultation with a nephrologist. The more common causes of glomerular hematuria are listed in Table 2.

Table 2. Common Causes of Glomerular Hematuria

- IgA nephropathy (Berger's disease)
- Thin glomerular basement membrane disease
- Hereditary nephritis (Alport's syndrome)

Berger's disease is the most common cause of asymptomatic glomerular microhematuria and, in the absence of significant proteinuria, typically follows a benign course. There is no proven treatment for the condition although fish oils may benefit patients with progressive disease.

Nonglomerular etiologies can be subdivided by location: the upper urinary tract (kidney and ureter) or the lower urinary tract (bladder and urethra) (Figure 4). The more commonly encountered upper and lower urinary tract etiologies are listed in Table 3. Although urothelial carcinoma involving the urinary bladder is the most common malignancy discovered in patients with asymptomatic microhematuria, benign processes are far more common than cancer. In particular, urinary tract infection (UTI), urinary tract stones, and benign prostatic hyperplasia (BPH) occur more frequently than urologic malignancies.

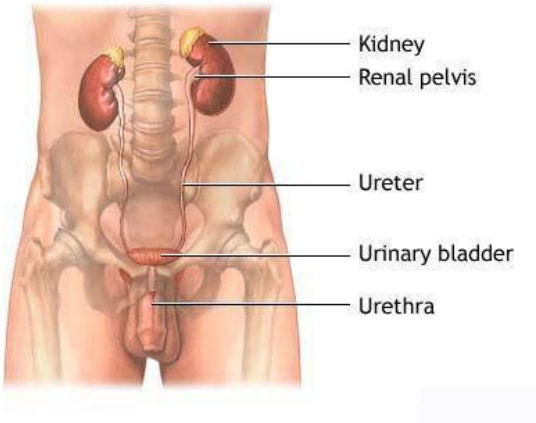

Figure 4. Human urinary tract anatomy that is at risk when hematuria is found. From: Nlm.nih.gov.

Table 3. Common Causes of Non-Glomerular Hematuria

Upper Tract

- Urolithiasis
- Pyelonephritis
- Renal cell carcinomas or other malignant/benign renal tumors
- Upper tract urothelial carcinoma
- Urinary obstruction (e.g. ureteropelvic junction obstruction, ureteral strictures)
- Trauma

Lower Tract

- Bacterial cystitis (UTI)
- Prostatitis
- Benign prostatic hyperplasia
- Strenuous exercise ("marathon runner's hematuria")
- Urothelial carcinoma of bladder/urethra
- Prostate cancer
- Instrumentation
- Trauma
- Radiation cystitis
- Benign hematuria (e.g. interstitial cystitis, trigonitis)

Oral anticoagulation therapy does not lead to *de novo* hematuria. However, the degree and duration of hematuria from another cause may be influenced by such therapy. The American Urologic Association guidelines require the same hematuria evaluation in patients on anticoagulation therapy as those without anticoagulation.

EVALUATION

As the differential for hematuria is quite broad, a thorough medical history and directed physical examination are necessary. It is imperative to determine if the patient has experienced gross hematuria or if the hematuria is purely microscopic, as the evaluation for these conditions may be different. The patient should be asked about the onset, duration, and associated symptoms of hematuria. The presence of flank pain, fever or urinary symptoms such as dysuria, frequency and urgency should be noted. Lower urinary tract symptoms in men, such as straining to void or nocturnal enuresis, may be indicative of BPH. Association with other activities (menses, physical exertion, etc.) may suggest an etiology for the patient's hematuria. Pelvic irradiation and certain chemotherapeutic agents, in particular cyclophosphamide and mitotane, have been associated with hemorrhagic cystitis. Both cigarette smoking and occupational exposures to aniline dyes and aromatic amines used in certain manufacturing processes increase the risk of bladder cancer, as does any sort of chronic irritation of the bladder (e.g. indwelling catheter, stones, and recurrent infections). Additionally, any prior history of urologic disease or interventions is an important aspect to discuss. The physical examination of patients with hematuria is invaluable. The presence of edema and cardiac arrhythmias may suggest the nephrotic syndrome. Costovertebral angle tenderness is suggestive of ureteral obstruction, often secondary to stone disease, in the afebrile patient. When fever and flank tenderness are both present the diagnosis of pyelonephritis should be entertained.

If the patient has not had a formal microscopic urinalysis this should also be part of the initial evaluation. As noted earlier, the dipstick urinalysis may yield false-positive results in patients with

myoglobinuria. Also, some patients may present with “red urine” relating to dietary intake or medication use (phenazopyridine) and these cases of spurious hematuria may reveal a normal microscopic urinalysis. Understand, however, that hematuria may be intermittent in patients with significant urologic disease. In addition to identifying the number of red blood cells per high powered field, the presence of white blood cells, bacteria, nitrites, and leukocyte esterase may suggest infection. If infection is suspected, a confirmatory urine culture should be obtained and a repeat urinalysis performed after the infection has been treated. A urine microscopy demonstrating microhematuria after appropriate treatment of a culture proven urinary tract infection mandates an evaluation. Patients with findings consistent with glomerular hematuria should be referred to nephrology for further evaluation.

All patients with hematuria should be evaluated by a urologist. Blood tests including renal function tests, complete blood count, and coagulation parameters can be useful, and PSA may be checked in men depending on their age, risk factors, and desire for PSA screening.

If patients have a history of gross hematuria, they require a comprehensive evaluation with cystoscopy, upper tract imaging (CT urography or MR urography), and urine cytology. To provide clarity for the evaluation of patients with microscopic hematuria, the AUA recently published the updated guideline which stratifies patients into low, intermediate, and high risk based on based on age, smoking history, and quality/quantity of hematuria (Table 4). Those categorized as low-risk should be engaged in shared decision-making with their urologists about the risks and benefits of further testing. At a minimum, they should have a repeat urinalysis in 6 months. Intermediate and high-risk patients should undergo a thorough urologic evaluation. Currently, urine cytology or other tumor markers are not routinely recommended in the evaluation of microscopic hematuria, but may be considered in patients who have persistent hematuria after a negative evaluation.

Table 4. AUA Microhematuria Risk Stratification

Low Risk
- Age: Women < 50 years old; Men < 40 years old
- Smoking history: Never or < 10 pack year history
- Urinalysis: 3-10 RBC/HPF

Intermediate Risk
- Age: Women 50-59 years old; Men 40-59 years old
- Smoking history: 10-30 pack year history
- Urinalysis: 11-25 RBC/HPF

High Risk
- Age: 60+ years old
- Smoking history: > 30 pack year history
- Urinalysis: > 25 RBC/HPF
- Gross hematuria

Because of the broad differential of urologic diagnoses that can cause hematuria, a complete evaluation of the urinary tract is indicated. Imaging studies are used to evaluate the upper urinary tract (kidneys and ureters) whereas the lower urinary tract is evaluated via direct endoscopy (Figure 5).

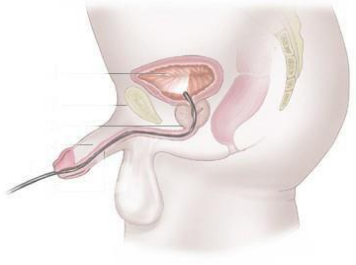

Figure 5. Flexible cystoscopy is used to examine the lower urinary tract in hematuria cases.

Imaging such as ultrasound or CT scans have limited sensitivity in diagnosing bladder masses and cannot identify urothelial erythema or carcinoma in situ, thus necessitating cystoscopy. Cystoscopy is an office-based procedure that does not require sedation. A flexible digital endoscopic camera is inserted into the bladder through the urethra. The entire urethra and bladder are viewed which includes the ureteral orifices and the intraurethral component of the prostate in men. This can allow for the diagnosis bladder tumors concerning for malignancy (Figure 6), urethral strictures, bladder stones, or prostatic enlargement.

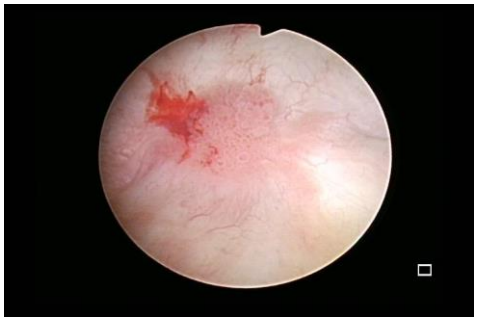

Figure 6. Bladder tumor concerning for urothelial carcinoma found on cystoscopy. From: https://university.auanet.org

The upper urinary tract including the ureters and kidneys are evaluated with imaging. Renal ultrasound can be utilized in intermediate risk patients to evaluate for renal masses and intra-renal stones; however, ultrasound cannot fully evaluate ureteral anatomy and may fail to identify all upper tract stones. A multiphasic contrasted CT scan of the abdomen and pelvis is utilized to evaluate the entire upper urinary tract. Also known as CT urography, this scan includes three phases (Figure 7). The first, non-contrasted phase, allows for the identification of renal or ureteral stones. The second, a contrast arterial/venous phase, can characterize renal masses. The third is a delayed phase which is obtained ~15 min after contrast administration. Delayed imaging allows for contrast excretion by the kidneys which then opacifies the urinary collecting system (renal calyces, renal pelvis, and ureters; Figure 7). Any filing defects in the collecting system may be concerning for upper tract urothelial carcinoma. If renal function or iodine allergies preclude the ability for the patient to receive contrast with their CT scan, then MR urography can be performed.

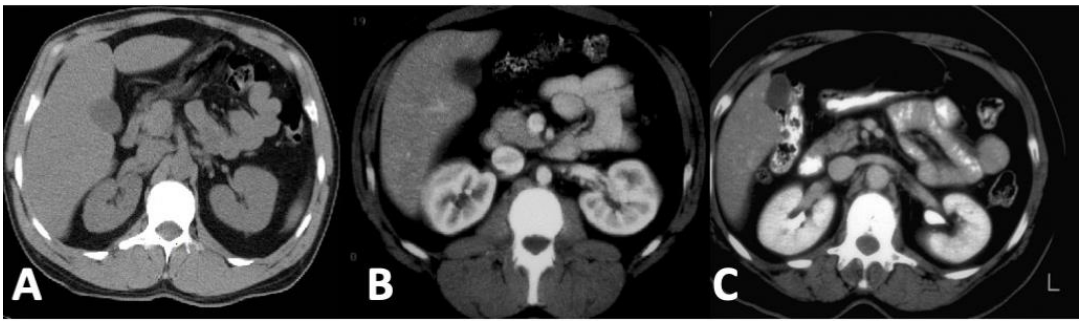

Figure 7. Tri-phasic CT Urography with non-contrasted (A), contrasted (B), and delayed (C) phases. From: https://university.auanet.org

With this evaluation strategy, a cause for hematuria is identified in roughly 57% of patients with asymptomatic microhematuria and 92% of patients with gross hematuria. Malignancy is identified in approximately 3-5% of patients presenting with asymptomatic microhematuria and 23% of patients presenting with gross hematuria. Following an unrevealing work-up for hematuria, a urinalysis should be repeated in a year. If repeat urinalysis is negative, no further workup is required.. Patients with persistent asymptomatic hematuria after a negative initial evaluation, physicians and patients discuss the merits of a repeat workup as some patients may benefit or request further evaluation.

SUMMARY:

1. Hematuria is categorized as either gross (visible to naked eye) or microscopic (diagnosed on microscopic urinalysis).
2. A positive dipstick for hematuria requires confirmatory midstream microscopic urinalysis.
3. The differential for hematuria is broad and includes glomerular and non-glomerular etiologies, the latter of which can be divided into upper and lower urinary tract origins.
4. A through history and physical examination, which should include risk factors for urothelial carcinoma, are utilized for risk stratification.
5. A complete urologic workup for hematuria includes cystoscopy and imaging of the upper urinary tracts.

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