

MODULE 5: HEMATURIA

KEY WORDS: Hematuria, Cystoscopy, Urine Cytology, UTI, bladder cancer

LEARNING OBJECTIVES

At the end of this clerkship, 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 finding malignancy during evaluation of hematuria.
4. Explain the significance of finding red cell casts in patients with microscopic hematuria.
5. Discuss the evaluation of hematuria.
6. Identify the indications for screening urinalyses in the general population.

DEFINITION

Hematuria is defined as the presence of red blood cells in the urine. When visible to the patient, it is termed gross hematuria, while microscopic hematuria is not visible to the naked eye but rather detected by the microscopic examination of the urinary sediment.

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. Dipsticks have a sensitivity of 95% and a specificity of 75% and positive results need to be confirmed with a microscopic examination of the urine as patients may test positive when there is not true blood there. Free hemoglobin, myoglobin and certain antiseptic solutions (povidone- iodine) will give rise to these false positive readings. Knowing the serum myoglobin level and results of the microscopic urinalysis will help differentiate these confounders. 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.

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.

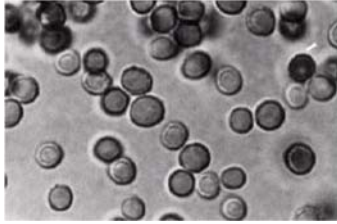


Figure 1: Red blood cells observed on high power microscopy of urine sediment.

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

EPIDEMIOLOGY

The prevalence of microscopic hematuria ranges from 1-20% depending on the population studied. The likelihood of finding significant urologic disease in these patients also 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 chemical exposure (cyclophosphamide, benzenes, aromatic amines)
- History of pelvic radiation
- Irritative voiding symptoms (urgency, frequency, dysuria)
- Prior urologic disease or treatment

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 (Figure 2).

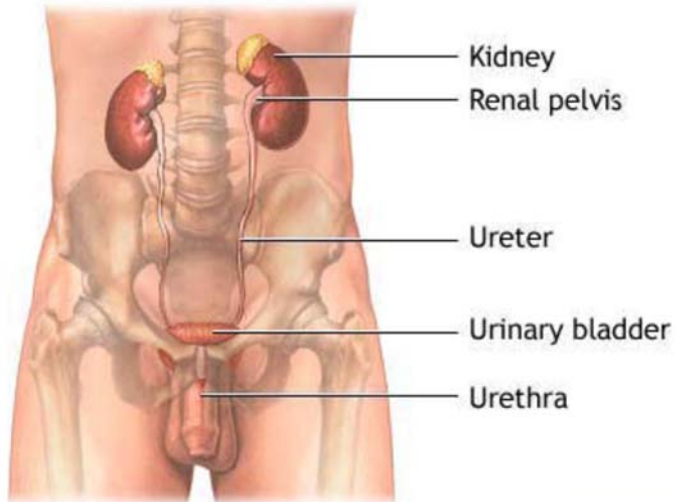


Figure 2: Human urinary tract anatomy that is at risk when hematuria is found. From: Nlm.nih.gov

Causes of hematuria may be generally grouped into the site of origin: **Glomerular or Nonglomerular**. Glomerular causes generally arise from the kidney itself. Nonglomerular etiologies can be further subdivided by whether the process is located in the upper urinary tract (kidney and ureter) or lower urinary tract (bladder and urethra) (Figure 2). In general, urologists are concerned with structural and pathologic conditions that are visible on imaging and endoscopic examination whereas glomerular hematuria is the purview of nephrologists.

Urinary findings suggestive of a glomerular source for the patient's hematuria include red cell casts, dysmorphic red blood cells (Figure 3) and significant proteinuria.

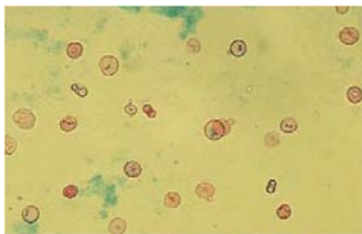


Figure 3: Example of dysmorphic red blood cells consistent with renal or glomerular hematuria.

The presence of red cell casts (Figure 4) in the urinary sediment is strong evidence for glomerular hematuria.



Figure 4: 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. A more comprehensive list is found in references 2 and 4.

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.

Causes of non-glomerular hematuria are often classified by location. The more commonly encountered upper and lower urinary tract etiologies are listed in Table 3. Although transitional cell carcinoma involving the urinary bladder is the most common malignancy discovered in patients with asymptomatic microhematuria, a benign process is far more the more likely explanation for the problem. In particular, urinary tract infection, urinary tract stones and prostatic enlargement occur more frequently than urologic malignancies.

Table 3 - Common Causes of Non-Glomerular Hematuria Upper Tract

- Urolithiasis
- Pyelonephritis
- Renal cell cancer
- Transitional cell carcinoma
- Urinary obstruction
- Benign hematuria Lower Tract
- Bacterial cystitis (UTI)
- Benign prostatic hyperplasia
- Strenuous exercise ("marathon runner's hematuria")
- Transitional cell carcinoma
- Spurious hematuria (e.g. menses)
- Instrumentation
- Benign hematuria (e.g. interstitial cystitis, trigonitis)

Excessive anticoagulation from 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. American Urologic Association guidelines suggest urologic and nephrogenic evaluation in patients with hematuria on anticoagulation therapy.

EVALUATION

The cornerstone of evaluating patients with hematuria is a thorough medical history and directed physical examination. A prior history of urologic disease or interventions is an important feature. Also, the presence of flank pain, fever or urinary symptoms such as dysuria, frequency and urgency should be noted. 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 (eg indwelling catheter, stones, and recurrent infections).

The presence of edema and cardiac arrhythmias may suggest the nephrotic syndrome and atrial fibrillation (with the possibility of renal embolization), respectively. 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, etc 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. Patients with findings consistent with glomerular hematuria should be referred to nephrology for further evaluation.

Based on the history and physical examination, including the urinalysis, patients with non- glomerular hematuria may be stratified as high risk or low risk for significant underlying urologic disease. Patients with gross hematuria or those with asymptomatic microscopic hematuria and any of the risk factors noted in Table 1 are considered high risk and should undergo a thorough urologic evaluation. Patients with asymptomatic hematuria and no associated risk factors are classified as low risk yet still warrant a complete evaluation. 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.

Because of the significant diseases that can cause nonglomerular hematuria, a complete evaluation of the urinary tract is indicated. Imaging studies are used to evaluate the upper urinary tract (kidneys and ureters) whereas direct endoscopic visualization of the bladder and urethra are needed for the lower urinary tract (Figure 5).



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

Cystoscopy is recommended by the AUA guidelines in all patients at least 35 years of age with microhematuria and in all patients who present with gross hematuria. For patients less than 35 years of age with microhematuria, cystoscopy may be performed at the discretion of the clinician based on the presence of risk factors for malignancy. Currently urine cytology or other tumor markers are not routinely recommended in the evaluation of asymptomatic microhematuria, but may be considered in patients with risk factors.

Delayed excretory cross-sectional abdominal and pelvic imaging is necessary to evaluate the upper urinary tract and exclude upper tract malignancies. Given its relatively high sensitivity and specificity, CT urography (CTU) is the preferred modality. If renal function or iodine allergies preclude the ability to undergo CTU, then MR urography or retrograde pyelograms with non-contrasted renal imaging can be considered.

With this evaluation strategy, a cause for hematuria is identified in roughly 57% of patients with microhematuria and 92% of patients with gross hematuria. Malignancy is identified in approximately 3-5% of patients presenting with microhematuria and 23% of patients presenting with gross hematuria. Following an unrevealing work-up for hematuria, a urinalysis should be checked annually. Patients with persistent hematuria after a negative initial evaluation warrant repeat evaluation in 3-5 years, especially in those with risk factors for urologic malignancy.

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