

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 four risk factors that increase the likelihood of finding malignancy during evaluation of microhematuria.
4. Explain the significance of finding red cell casts in patients with microscopic hematuria.
5. Contrast the evaluation of hematuria in the low risk patient with that of high-risk patient.
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 and is usually alarming to patients. Microscopic hematuria is that detected by the dipstick method or 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 should be confirmed with a microscopic examination of the urine. Free hemoglobin, myoglobin and certain antiseptic solutions (povidone-iodine) will also give 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.

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. The sediment is resuspended 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 two of three specimens.

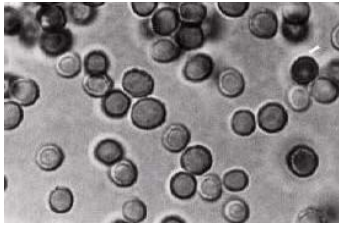


Figure 1: Red blood cells observed on high power microscopy of urine sediment.

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

- Age >40 years
- 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 approximately 10%, 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).

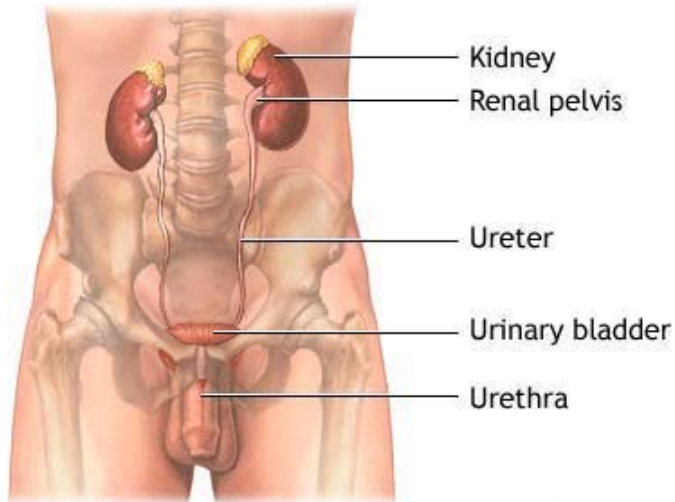


Figure 2: Human urinary tract anatomy that is at risk when hematuria is found. From: Georgetown Hospital Website Anatomy and Function of the Urinary System

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.

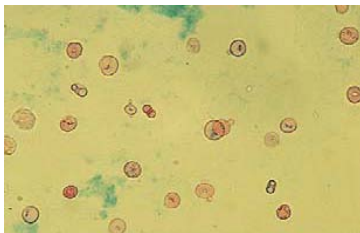


Figure 3: Example of dysmorphic red blood cells consistent with renal or glomerular hematuria.

The presence of red cell casts 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 more often the source of 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

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.

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.

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 urinalysis. Understand, however, that hematuria may be intermittent in patients with significant urologic disease and a repeat urinalysis should be obtained if clinical suspicion is present.

In addition to identifying the number of red blood cells per high-powered field, the presence or absence of red cell casts and/or dysmorphic red blood cells, the presence of white blood cells and bacteria in the urinalysis 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 nonglomerular hematuria may be stratified as high risk or low risk for significant underlying urologic disease. Patients with gross hematuria or those with 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.

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 urine cytology or direct endoscopic visualization of the bladder and urethra are needed for the lower urinary tract (Figure 5). The diagnostic studies selected depend on the risk factors for significant disease.-



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

In low risk patients, renal ultrasonography and voided urine cytology are appropriate screening studies for hematuria. Ultrasound examination of the kidneys will detect and characterize renal masses larger than 1 cm in diameter. Also, clinically significant nephrolithiasis is likely to be found by ultrasound. Although the ureters are difficult to image with ultrasonography, proximal hydronephrosis (dilation) or unilateral absence of a “ureteral jet” of urine into the bladder suggest ureteral obstruction and the need for additional studies. Cytologic examination of a voided urine specimen is helpful to detect urothelial cancer. Remember that urine cytology does not screen for renal cell

cancer (a reason for renal imaging) and may reveal false negatives in the case of low-grade transitional cell cancers. Conversely, positive urine cytology is usually indicative of transitional cell cancer and follow-up endoscopic examination is necessary for a definitive diagnosis, and for localization and staging. Low-risk patients may prefer to proceed directly to cystoscopy, which is acceptable.

Patients with gross hematuria or associated risk factors should undergo contrast-enhanced imaging of the kidneys and ureters in addition to cystourethroscopy and urine cytology. Previously, the intravenous pyelogram (IVP) was the standard upper tract imaging study for hematuria. However, this has been largely replaced by computerized tomography (CT) scanning of the abdomen and pelvis after administration of intravenous contrast. CT scanning is superior in differentiating cystic from solid masses within the kidney compared to the IVP. Significant information about non-urologic structures is also provided on CT imaging. Non-contrast helical CT scanning of the abdomen and pelvis is now the method of choice for detecting renal calculi. Before ordering any contrast study (IVP or contrast-enhanced CT scan), the patient's medications and allergies should be reviewed and normal renal function documented.

If imaging studies suggest calyceal or ureteral pathology, then cystoscopic examination may be performed in the operating room where retrograde ureterograms can be done under fluoroscopic guidance. If imaging studies are normal, then cystoscopy is performed in the office with topical anesthesia. At the time of cystoscopy, a "bladder wash" (barbotage) can be sent for cytology, as the yield from this test is higher than that of a voided urine specimen.

With this evaluation strategy, a cause for hematuria is identified in over 80% of cases. Depending on their risk, up to 20% of patients with asymptomatic microhematuria are discovered to have a urologic cancer. Patients with persistent hematuria after a negative initial evaluation warrant repeat evaluation at 48-72 months since 3% of this group will be subsequently diagnosed with a urologic malignancy. Despite these findings, please remember that there are no evidence-based recommendations for screening asymptomatic patients for hematuria.

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