Defining and Diagnosing Hematuria

Only a tiny minority of patients with benign hematuria will have a condition that is life-threatening or warrants treatment.

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The incidence of renal tumors in an adult population is about one in 10,000, with 0.5% to 1% of a normal population having some glomerular disorder. Hematuria, therefore, is more likely to be of renal origin than urologic origin.

Microscopic hematuria, which is picked up on urinalysis, is present when more than five red blood cells (RBCs)/high power field (hpf) are found. This condition is very common.[1,2] The strict definition of hematuria is when more than two RBCs/hpf are found, but this is over-sensitive and, therefore, will pick up many false-positives.

Urine should be examined when it is fresh, preferably within 30 minutes of being taken. The process is best performed when the urine is concentrated. This collection methodology is recommended because red cells lyse over time, and a dilute urine will negatively affect the concentration of all cellular constituents in the urine.

Dipstick testing is the initial test for detecting hematuria. It is very sensitive and will pick up one to two RBCs/hpf. Dipstick testing will register positive in a urine that has microscopic hematuria allowed to stand for too long (*i.e.*, with hemolyzed RBCs) in spite of few or no red cells being seen on the film. If the dipstick is positive, urine should be sent for urinalysis. If

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the patient has more than five RBCs/hpf, microscopic hematuria is present.

Prior to referring a patient with microscopic hematuria for nephrology or urology assessment, it is worth repeating the urinalysis, as hematuria may occur after simple conditions, such as a viral illness or after exercise. If the test remains positive, referral may have to be considered.

Red cell morphology has received considerable attention over the past 20 years. Red cells that originate in the glomeruli become distorted as they travel through the nephron and assume various odd shapes (dysmorphic RBCs), which can be identified under a phase-contrast microscope by an experienced technician or nephrologist.[3] The way a technician or nephrologist perceives them, however, can vary.[4] Some patients with biopsy-proven glomerulonephritis have no dysmorphic RBCs. Dysmorphic red cells also may be seen in a urine that started off with normal RBCs, but was allowed to stand for too long. Testing for dysmorphic RBCs, therefore, is best arranged by a nephrologist.

Causes of Hematuria

There are many causes of hematuria, which are given in Table 1. Hematuria with proteinuria signifies non-urologic causes that should be investigated further (unless it is transient, as in fever, *etc.*). Microscopic hematuria without significant proteinuria, however, may be found in mild glomerular disease. Hematuria is virtually never a presenting feature in people with coagulopathies and is rare in patients on anticoagulants.[5] Hematuria may be found with an indwelling catheter or within a few hours of straight catheterization. Interpretation of urinalysis in that situation is impossible. The presence of casts (cellular or granular) in urine signifies the presence of renal disease.

Macroscopic hematuria is far more likely to be associated with identifiable significant disease, as compared with microscopic hematuria. It may be associated to renal pain (*i.e.*, as in carcinoma or polycystic kidneys) or even clot colic. It always requires full evaluation. Immunoglobulin A (IgA) glomerulonephritis (Berger's disease) may produce hematuria without significant proteinuria.

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Major Points

- Microscopic hematuria is most likely renal in nature rather than urologic.
- Casts in urine with or without proteinuria signal a renal etiology.
- If the etiology is renal in nature, check renal function and refer the patient to a nephrologist.
- Microscopic hematuria, with everything else being normal, signals benign hematuria (almost certainly).
- Microscopic hematuria is common.
- Microscopic hematuria is harmless.
- Microscopic hematuria is probably not worth a referral to a urologist if the patient is younger than 50.

Table 1

Causes of Hematuria

Disease	Notes
Intrinsic Renal Disease	
• Glomerulonephropathy - Primary - Secondary (*i.e.,* collagen vascular, diabetes) - Benign	• May occur with proliferative or non-proliferative glomerulonephritis (GN) (*i.e.,* diabetes); usually more than 1 g/L proteinuria.
• Cystic disease - Simple - Polycystic - Medullary sponge	
• Renal tumors	
• Interstitial disease - Interstitial nephritis - Papillary necrosis/analgesics - Stones or crystals - Acute infection	• May have pyuria (polys or eosinophils). • Pyuria present. • Often have infection. • Always pyuria.
• Structural - Atrioventricular malformation	
Non-Renal Disease	
• Ureteric - Stones - Tumor	
• Bladder - Tumors - Stones - Cystitis	• May not have pyuria.
• Prostate - Carcinoma - Prostatitis	
• Urethral lesions	

History and Physical

If hematuria is found, the following should be included in the history:

- Previous stones;
- Analgesic intake;
- Trauma;
- Previous hematuria;
- Edema;
- Hypertension;

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The physical examination should include taking the patient's blood pressure, as hypertension is found in over 50% of patients with intrinsic renal disease.

- Family history of renal disease (*i.e.*, polycystic, familial glomerulonephritis).

The presence of deafness in a family could suggest Alport's syndrome, which is a type of glomerulonephritis. Other items that should be elicited include pain, weight loss, fever of unknown etiology and previous urinary infections. Hematuria itself is never a manifestation of urinary tract infections (white blood cells will always be found).

The physical examination should include taking the patient's blood pressure, as hypertension is found in over 50% of patients with intrinsic renal disease. Hematuria may occur when blood pressure control is very poor. Prostate size, consistency and tenderness also should be assessed. Finally, renal enlargement (as in polycystic kidneys) must be covered by the physician.

Investigations

If hematuria is found (on more than one occasion) without any other urinary abnormality, then serum creatinine should be checked. If serum creatinine is raised, refer to a nephrologist. If serum creatinine is normal, an intravenous pyelogram (IVP) or renal ultrasound should be obtained. In addition, the physician should send the urine for cytology. If all of these investigations are negative, a conservative approach is warranted involving patient follow-up every few months (see section on benign hematuria). Although many physicians refer such patients to a urologist, the vast majority of these cases will have normal urologic investigations.[6]

If other urinary abnormalities, such as casts and proteinuria, are found, serum creatinine should be measured and an IVP (if the creatinine is normal) or renal ultrasound (if the creatinine is raised) should be obtained. Referral to a nephrologist is also suggested.

If microscopic hematuria and pyuria are present, urine culture should be checked. In high-risk patients (*i.e.*, alcoholics, native people), three early morning urines should be checked for tuberculosis.

Miscellaneous Conditions Causing Microscopic Hematuria

Transient hematuria may be found during mild viral or bacterial illness (mechanism unclear).

This is often accompanied by mild proteinuria. Vigorous exercise may induce microscopic hematuria and, occasionally, macroscopic hematuria.[7] The mechanism is unclear. Evidence exists for both glomerular and bladder bleeding after exercise, which is always self-limiting. Hypercalciurea in children has been found to be associated with microscopic hematuria,[8] presumably related to stones that are too small to detect or due to crystal formation.

Benign Hematuria

When all investigations are negative and the patient simply has microscopic hematuria, the patient falls into the diagnostic description of "benign hematuria." This diagnosis includes several different nephrologic and urologic entities. Virtually all of these have certain features in common. The patients do not develop, nor have, significant renal disease that will cause renal failure or hypertension in the future. In the case of urologic conditions, almost all of these conditions are benign.[1,7]

Between 10% and 20% of the general population will have isolated hematuria,[1,2] the majority of which will be benign. In the studies that have studied patients' biopsies,[9] none of the various histologic types of glomerulonephritis found warranted therapy. Furthermore, progression to significant renal failure was not found. Glomerular abnormalities are found in approximately 50% of such patients, however, this is a controversial number because of the clear-cut referral bias in some of the published papers These abnormalities include IgA nephropathy in most, as well as other types of glomerulonephritis. Half of these biopsies will be entirely negative. In almost all cases referred to a urologist (98%), nothing of significance is found.[1,7] Only 0.5% have a neoplasm, which usually occurs in older patients or in high-risk patients (*i.e.*, patients working with amiline dyes, heavy smokers, strong family history of carcinoma).

Based on multiple studies, it is perfectly appropriate not to refer the patient who is younger than 50, who has no other abnormality other than microscopic hematuria (*i.e.*, normal renal function and negative radiologic investigations), or who is not at high risk. Even in patients over 50, it is probably unnecessary to get a urologic opinion. These patients, however, should be followed two to three times each year to ensure nothing else is developing.

In summary, only a tiny minority of patients with benign hematuria will have a condition that is life-threatening or warrants treatment. CME

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