What is significant hematuria for the primary care physician?

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Hematuria is a common finding in primary care practice. Causes of significant hematuria include urinary tract infection, urolithiasis, malignancies, benign prostatic hyperplasia, and nephropathies. Hematuria is identified by taking a patient history and by performing a routine urine dipstick test. If a patient has a history of gross hematuria and/or a positive urine dipstick test, he or she should then have a microscopic urinalysis. The primary care physician can order ancillary tests such as laboratory tests to assess renal function, and possible imaging tests such as ultrasound, computed tomography urography, or magnetic resonance urography. The patient may be referred to a nephrologist or urologist for further assessment if required. Cystoscopy may be considered. Even if the patient has a negative work up, guidelines recommend that primary care physicians follow the patient semi-annually for 3 years.

Key Words: referral, hematuria, primary care, laboratory tests, imaging, cystoscopy

Introduction

Hematuria is a clinical finding that is commonly encountered by primary care physicians and urologists. Although it is common, it should not be ignored, because roughly 4% of patients with microscopic hematuria and up to 40% of patients with gross hematuria could be harboring a malignancy.[1] Those percentages represent a significant number of patients in a busy clinical practice. Practicing physicians will generally have at least one and perhaps several patients whose lives are changed because their hematuria was investigated and evaluated. Therefore, it is important to effectively and efficiently manage patients who have hematuria.

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What is significant hematuria?

When confronted with a patient with hematuria, a clinician must establish whether the hematuria is clinically significant. This will allow a primary care physician and/or specialist to begin an appropriate work up in these patients. Gross hematuria should always be considered significant, and it may also be regarded as a sign of malignancy until proven otherwise. It is important that the patient's clinical history corroborates that the blood originates from the urinary tract. A history of "red urine" does not always equate with the presence of blood, see Table 1.[2] Patients should be questioned to provide a complete clinical history, possibly with a family member present. Questioning someone who witnessed the patient's hematuria may be helpful. The passage of blood clots during urination is a good confirmatory detail. If the patient is female, a gynecological history may help rule out hematuria arising from vaginal bleeding. If

TABLE 1. **Common causes of red urine**[2]

With a positive dipstick for blood
- Hematuria
- Hemoglobinuria
- Myoglobinuria
- Menstrual contamination

With a negative dipstick for blood

Foods
- Beets
- Berries
- Food coloring

Drugs
- Aminosalicylic acid
- Ibuprofen
- Laxatives containing phenolphthalein or senna
- Methyldopa
- Phenazopyridine
- Phenothiazines
- Rifampin

the patient's clinical history confirms the presence of hematuria, further questions may localize the source of bleeding. If gross hematuria appears throughout the urinary stream, then it probably originates above the level of the bladder outlet, including the upper urinary tract and kidneys. If blood is detected only at the initiation of urination, then it is likely from the urethra. Gross hematuria at the end of urination may be from the prostate or bladder neck. Taking an inventory of associated symptoms may help generate a differential diagnosis. For example, flank pain, nausea, and hematuria suggest a renal colic attack. Pain, mass, and hematuria use to be considered the classic triad for the suspicion of renal cell cancer. However, today most cancers are found serendipitously at the time of an abdominal ultrasound.[2] Even if further details are missing, the presence of gross hematuria necessitates further evaluation and/or referral to a specialist.

Microscopic hematuria is a more common finding than gross hematuria. The reason for significant microscopic hematuria can be more difficult to determine. Microscopic hematuria is often detected from a positive urine dipstick test. Although a dipstick test is a convenient, rapid, point-of-care test, it has pitfalls. Dipsticks are based on a chemical reaction between the dipstick reagent and substances in the urine that produces a color change. The color change can be affected by factors affecting the dipstick reagent, urine, or their interaction. Therefore, microscopic urinalysis is recommended to confirm a positive dipstick test for hematuria.[3] In microscopic urinalysis, urine is centrifuged, most of the supernatant is poured off, and the sediment is re-suspended in the residual supernatant. The sediment aliquot is then examined under a microscope, using low- and high-power magnification. Microscopic urinalysis is more laborious than dipstick testing and was traditionally performed manually. More recently, this procedure has been automated to make it more rapid, reproducible, and accurate.[4]

In the Canadian guidelines, significant microscopic hematuria is defined as 2 or more red blood cells (RBCs) per high power field, confirmed in two microscopic urinalysis tests performed when there is no benign etiology such as menstruation, recent exercise, recent sexual activity, or recent instrumentation of the urinary tract.[5] T he American recommendations define significant microscopic hematuria as 3 or more RBCs per high power field in a properly collected specimen and in the absence of a benign etiology.[6] Physicians should make sure to use a consistent definition for significant microscopic hematuria.

Causes of significant hematuria

The identification of significant hematuria may trigger anxiety in patients and they may ask physicians about potential reasons for this finding. Primary care physicians need a working knowledge of the main etiologies of significant hematuria. They also need to consider initiating further investigations and, if needed, make a referral to a specialist.

Urinary tract infection

Microscopic hematuria is usually associated with urinary tract infections (UTIs) and can even cause gross hematuria, although this is less common. Patients with a UTI generally also have other voiding symptoms, especially dysuria and acute urinary frequency. It is important to remember that finding symptomatic hematuria and a positive urine culture in a patient should not always pre-empt the need for looking for other potential causes of the hematuria. However, referral to a urologist may generally be delayed when the patient has a positive urine culture. Treatment of the infection and repeat assessment of the urine should be conducted in this setting.

Urolithiasis

Kidney stones are common and both men and women may have them. They are a clinical problem that appears to be increasing in prevalence, requiring more sustained efforts in diagnosis, treatment, and prevention.[7]

Smaller stones that reside in the kidney are usually asymptomatic, and microscopic hematuria may be the only manifestation. Larger stones, including staghorn calculi, may present with gross hematuria. Staghorn calculi may be associated with the presence of UTIs when the urine is infected with a urease-producing organism such as Proteus. Hematuria associated with the acute onset of lateralizing flank pain is the classic presentation of a stone that moves into the ureter.

Malignancies

Urological malignancies are potentially serious. A high index of suspicion and careful evaluation of patients with hematuria will ensure that any malignancy is diagnosed quickly. With the widespread use of abdominal ultrasound, most renal cell carcinomas are found as an incidental mass at the time of imaging. Microscopic hematuria is common in these situations. Gross hematuria is not as common, but it may be seen if the patient has a larger mass located more centrally in the kidney.

Urothelial carcinoma arises from the lining of the collecting system. Gross hematuria tends to be the most common symptom with this type of tumor. Patients who have a tumor that arises from the renal pelvis or ureter may present with flank pain, and they may note the passage of "worm-like clots" on micturition. Lesions arising from the bladder often cause no pain, but patients with these lesions may have large blood clots when they urinate.

Although incidental microscopic hematuria may be present when prostate cancer is diagnosed, this hematuria is more likely due to benign prostatic hyperplasia (BPH) rather than the cancer. Typically, prostate cancer does not cause hematuria unless it is in more advanced stages. In advanced or metastatic prostate cancer, hematuria is often associated with other constitutional and obstructive urinary symptoms. Successful treatment of prostate cancer will often eliminate or significantly reduce the severity of any hematuria.

BPH

BPH commonly and progressively afflicts men as they age. While the classic patient presentation is usually that of lower urinary tract obstructive or irritative symptoms, hematuria is also common. BPH may, in fact, be the most common cause of microscopic hematuria in men. Less commonly, BPH may be the sole cause of gross hematuria and clot retention. A diagnosis of BPH can be made only after full urological evaluation and exclusion of other causes of hematuria.

Nephropathies and nephritis

The medical causes of hematuria should not be overlooked. This is particularly true in the presence of microscopic hematuria in children. Patients with nephropathies and nephritis may present with hypertension, edema, and renal insufficiency, and urine tests may reveal the presence of proteinuria and RBC casts. When appropriate, the primary care physician should consider consulting a nephrologist. Since smoking can lead to immunoglobulin A (IgA) glomerulonephritis and microscopic hematuria, it is always important to ask patients about smoking when taking a clinical history.

Patient management

In the physician's office, hematuria can be identified by a patient's clinical history—a complaint of gross hematuria—and/or findings from a routine urine dipstick test. Physicians should take a thorough clinical history. They should assess a patient for factors placing them at higher risk of significant urological disease. These include age older than 40 years; past or current analgesic abuse, smoking, or exposure to chemicals or dyes (benzenes or aromatic amines); or history of pelvic irradiation, gross hematuria, irritative voiding symptoms, or UTIs.[5] The patient's current medications or prior urinary tract interventions might be linked to the bleeding, see Table 2.

To do a urine dipstick test, the patient should be instructed to provide a fresh, midstream urine sample, and the sample should not be left for more than 2 hours at room temperature before it is tested.

TABLE 2. **Medications and interventions associated with hematuria**

Medications

- Penicillins, aminoglycosides, cephalosporins
- Amitriptyline
- Cyclophosphamides
- NSAIDs
- Rifampin

Interventions

- Recent surgery for urolithiasis
- Urinary tract stenting
- Transurethral procedures of the lower urinary tract
- Transrectal biopsy of the prostate
- Genitourinary radiation therapy
- Bacillus Calmette-Guerin installations for bladder cancer
- Bladder instillations for interstitial cystitis

Pre hydration is also beneficial, particularly in children. The dipsticks should not have passed their expiry date, and they should have been stored at the correct temperature. To perform the test, the dipstick should be quickly and completely immersed into the urine specimen, and then it should be tapped on its edge to remove excess urine and to reduce the mixing of reagents from different test pads on the dipstick. If the patient has microscopic hematuria, then the urine dipstick test will show a positive color reaction. The physician should also look for significant urine protein on the urine dipstick test, which may suggest nephrologic disease.

When confronted with a convincing history of gross hematuria and/or a positive dipstick result, the physician should request a microscopic urinalysis and ensure that the patient collects a urine specimen after waiting at least 48 hours after menstruation, vigorous exercise, or sexual activity. The physician needs to pay attention to the number of RBCs and their morphology, since this may identify undiagnosed renal conditions. The patient can be referred to a urologist or a nephrologist, as needed, for further evaluation.

Ancillary studies

Patients with significant hematuria will need to be referred to an appropriate specialist. Although such specialists will be initiating their own work up, the primary care physician should first order some basic ancillary tests. Doing this will significantly facilitate a timely assessment for their patients.

Laboratory investigations

Suggested laboratory investigations include blood urea nitrogen (BUN), serum creatinine, and estimated glomerular filtration rate (eGFR), which will indicate the patient's overall renal function. If tests show that a patient's renal function is compromised, this suggests that he or she may need a nephrologic assessment, to look for kidney impairment and for a non-urological cause for the hematuria. Knowledge of a patient's renal status is helpful in selecting imaging modalities during the patient work up process (as discussed later in this article). Examination of blood coagulation parameters (international normalized ratio [INR] and partial thromboplastin time [PTT]) may help explain the magnitude of the perceived hematuria and may identify a coagulopathy that needs urgent correction. Note, however, that a coagulopathy—whether it is primary or a result of medical therapy—should not be considered a sole cause for hematuria, so further investigation is strongly advised.[8] A coagulopathy may simply unmask underlying pathology more quickly. In women of reproductive age, it may be helpful to perform a serum beta-HCG test to rule out pregnancy, since pregnancy would affect the selection of imaging tests.

Urine cytology tests and determination of urine markers (e.g., bladder tumor antigen [BTA] stat, and nuclear matrix protein 22 [NMP-22]) should not be part of a routine evaluation. In general, there are large discrepancies in reports of the sensitivities and specificities of these tests.[9] The only instances where it may be reasonable to consider an ancillary urine test is in a patient with significant hematuria and a previous negative work up or a patient with risk factors for bladder cancer or carcinoma in situ. However, this can generally be left to the judgment of a urologist.

Imaging

Making didactic recommendations about appropriate urinary tract imaging can be challenging. Compared with laboratory testing, imaging studies are far more costly and labor intensive, which can be a burden on the healthcare system. In Canada, the remoteness of some practice locations does not allow for easy access to all imaging modalities. Moreover, there is very little literature about comparative, controlled studies of imaging in patients with hematuria.

Ultrasound: The use of ultrasound is considered a less-than-optimal choice for the investigation of hematuria. Ultrasound is mainly limited to investigating the renal parenchyma, and the sensitivity and specificity of ultrasound varies widely.[10-12] In practice, ultrasound is helpful for identifying large renal masses and stones. Although it is not the best type of imaging modality, ultrasound is still frequently used due to its widespread availability and its safety relative to other types of imaging. An intravenous urogram (IVU) may be requested, to provide some detail about the upper urinary tract anatomy, but is not commonly offered by most imaging departments nowadays, especially if computed tomography (CT) and CT urography is available.

CT urography (CTU): If it is available, CTU is the preferred form of diagnostic imaging for patients with hematuria. In noncomparative studies, CTU has the highest degree of sensitivity and specificity.[13,14] It is very rapid and can be performed in minutes when a multiphasic CT machine is used. Multiphasic imaging will give excellent information on baseline densities, which is important regarding urolithiasis. In addition, other phases can identify renal parenchymal masses, areas of trauma or scar, and filling defects within the collecting system. A CT scan may also identify other unusual causes of hematuria (e.g., renal artery

stenosis, abdominal aortic aneurysm) or may discover incidental non-related pathology. Aside from cost, drawbacks include radiation exposure, which can be particularly significant in children and in undiagnosed pregnancy. However, lower-dose protocols can be devised to deal with this issue. Renal impairment is another factor that may preclude this investigation because of the nephrotoxicity of intravenous contrast materials. An N-acetyl cysteine protocol including pre-hydration may be employed to counter nephrotoxicity in selected patients, but it is advisable to do so in consultation with a nephrologist. Contrast reactions have been reported, and in very rare instances, death has been attributed to contrast agents.

Magnetic resonance urography (MRU): MRU may be a suitable, though less effective imaging modality in patients where CT urography is contraindicated. MRU may be safer than CT urography, although patients may have a nephrotoxic risk from the gadolinium used in MR contrast studies. MRU is contraindicated in patients with devices such as pacemakers and aneurysmal clips. Moreover, MRU protocols are subject to considerable variation making interpretation of limited, comparative data difficult. When considering non-comparative data, it appears that MRU provides high sensitivity and specificity imaging of renal parenchyma, but is not as useful when imaging kidney stones or the collecting system.[15]

The choice of an imaging modality depends on several factors. Since ultrasound is widely available and nontoxic, it is reasonable to order this imaging test first. It is the authors' opinion that CTU should be ordered in patients with gross hematuria and possibly also in patients with microscopic hematuria who possess significant risk factors suggesting genitourinary pathology. The patient should either have no contraindication for the use of a contrast agent with CTU, or have a contraindication that can be appropriately managed. For example, N-acetyl cysteine prophylaxis can be given to a patient who has borderline renal function and few other medical comorbidities. Decisions regarding the use of MRU and retrograde pyelography can be delegated to a urologist who will likely have direct access to these resources.

Referring a patient to a urologist or nephrologist

Based on the preceding discussion, it seems quite reasonable that primary care physicians should refer all patients with significant hematuria to a urologist or nephrologist. Some physicians may argue that the rates of malignancy in younger patients (< 35 years of age) with hematuria are very low, so very few malignancies would be found after referrals to specialists following negative imaging tests. The authors would argue that these patients compose a much smaller proportion of patients with hematuria, so the absolute number of referrals resulting in normal findings is quite low. Moreover, imaging modalities performed on patients can vary, so we believe that a referral offers a more consistent patient evaluation, which can only benefit patients in the long run.

Referral to a nephrologist is helpful when a patient is found to have compromised renal function, proteinuria, and RBC dysmorphia/RBC casts. The latter may occur with concomitantly with other causes of hematuria as well, so it is important to consider involvement by urology as well.

To complete the patient's urology work up, cystoscopy may be considered. Cystoscopy is recommended for all adult patients with gross hematuria and significant risk factors. If a patient presents with asymptomatic microscopic hematuria and no risk factors, then cystoscopy should be done if the patient is older than 35 or 40.[2] In children, cystoscopy is best considered when gross hematuria is present. There is very low yield with cystoscopy in pediatric microscopic hematuria. Even if no malignancy is found, the urologist may discover other findings that could benefit the patient. For example, a young man with hematuria and lower urinary tract symptoms (LUTS) may be found to have a urethral stricture. In this case, cystoscopy would lead to a very treatable diagnosis and would result in a significant impact on quality of life.

Ongoing follow up

Even with a negative work up, patients are still concerned that their hematuria may be persistent and may evolve into pathology if left unchecked. The literature reports that 1%-3% of patients with a negative work up can develop a malignancy within 3 years.[5] As a result, it is reassuring to form a strategy that deals with these concerns. The American Urological Association best policy panel recommends that primary care physicians check for gross hematuria, new urinary symptoms, and positive cytology semi-annually for 3 years. If all is negative at that time, follow up may be discontinued. If not, then repeat evaluation should be performed.

Disclosure

The authors have no potential conflict of interest. □

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