Evaluation of an Abnormal Urinalysis in the Asymptomatic Patient

DOUGLAS M. LANDWEHR, M.D., PH.D.

Associate Professor of Medicine, Division of Nephrology, and Director, Hemodialysis Unit, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Physicians are occasionally presented with the problem of evaluating a patient who has an abnormal urinalysis[1] but who has no other sign or symptom of genitourinary (GU) tract disease. For example, patients may present with hematuria, pyuria or slight proteinuria, but they may have no other clinical or laboratory abnormality to suggest glomerulonephritis, renal failure, urinary tract infection, obstruction, hypertension, or stones. There are a wide variety of lesions which may produce such isolated abnormalities,[2,3] and a rational approach is indispensable in preparing an efficient and definitive diagnostic plan.

The urinalysis may be abnormal because of the presence of red blood cells, white blood cells, or excessive amounts of albumin. To understand the diagnostic possibilities of such abnormalities it is useful to begin by considering the sensitivity of the routine urinalysis (Table 1). Detection of the presence of only 1+ albuminuria requires albumin in a concentration of 30 mg/100 ml. In the case of red cells and white cells in a centrifuged urine specimen, our limits of detection extend to recognition of a single cell under the microscope. Let us next consider the quantity of each of these elements in a single milliliter of blood. Blood normally contains 4 gm of albumin per 100 milliliters, which is equivalent to 40 mg/ml. White blood cells number approximately 10,000/mm^3 of blood, which is equivalent to 10 million/ml. Similarly, 5,000,000 red blood cells per mm^3 of blood is equivalent to 5 billion/ml. Let us assume that some abnormality in the GU tract leads to the loss of 1 ml of blood (a relatively small amount) into the urine each day. Assuming a modest urine volume of 1,000 ml/day, let us then examine what would be the concentration of the individual components of the urine relative to the limits of detection. In the case of albumin, 40 mg from 1 ml of blood distributed in one liter of urine would result in a concentration of only 4 mg/100 ml. This is well below our detection limit of 30 mg/100 ml for a 1+ measurement. White cells from 1 ml of blood distributed in 1,000 ml of urine would result in a concentration of 100,000/10 ml. If one takes 10 ml of that urine, as with the standard urinalysis, centrifuges it and resuspends the sediment, all 100,000 white cells are potentially identifiable; with red blood cells, there would be an even higher number of identifiable units in the urinalysis.

There are certain important conclusions concerning the routine urinalysis which can be drawn from the above consideration: on one hand, it is evident that we can detect small amounts of bleeding into the urine by the presence of red blood cells; on the other hand, relatively large amounts of blood, 20-40 ml/day, depending on urine volume, must be present to give detectable albuminuria. Such quantities would contain large numbers of red blood cells and thus result in gross hematuria. Albuminuria, detected on the routine urinalysis and accompanied by only microscopic hematuria, could, therefore, not reflect simple bleeding in the GU tract. Albumin can be separated from blood cells only in the glomerulus and, thus, glomerular abnormalities must exist if there is detectable albuminuria in the routine urinalysis in the absence of gross hematuria.

Correspondence and reprint requests to Dr. Douglas M. Landwehr, Division of Nephrology, Box 197, Medical College of Virginia, Richmond, VA 23298.

MCV QUARTERLY 14(3):140-143, 1978

TABLE 1
Sensitivity in Detection of Abnormalities of the Urinalysis

	Albumin	Pyuria	Hematuria
Limits of detection	30 mg/100 ml	1 WBC/HPF	1 RBC/HPF
Content in 1 ml blood	40 mg/L (4.0 gm/100 ml)	10,000,000 (10.000/mm^3)	5,000,000,000 (5,000,000/mm^3)
Concentration when 1 ml blood mixed with 1 liter urine	40 mg/L (4.0 gm/100 ml)	10,000,000/L 100,000/10 ml	5,000,000,000/L 50,000,000/10 ml

In view of the above considerations, let us now consider the evaluation of the patient with an abnormal urinalysis. Asymptomatic albuminuria, with or without microscopic hematuria, indicates glomerular leakage of protein. As we are considering asymptomatic albuminuria, this would involve only mild degrees of protein loss. Proteinuria greater than 3.5 gm/day would not be asymptomatic or isolated, since it would be accompanied by manifestations of the nephrotic syndrome. Causes of asymptomatic albuminuria may be divided into functional and pathological disturbances. It is referred to as functional when it is not permanent and when it occurs in association with other temporary physiological disturbances. Examples of this include albuminuria which occurs with fever, exacerbations of congestive heart failure, or severe exertion. Another kind of functional proteinuria is that which is detectable in certain persons after prolonged standing. Such postural or orthostatic proteinuria usually involves excretion of less than 1.5 gm of protein per day. Long-term follow-up of most patients with postural proteinuria have indicated a good prognosis; however, in somewhat less than 10% of cases, postural proteinuria is associated with unequivocal glomerular disease, and here the prognosis is more guarded.

Asymptomatic albuminuria also occurs as a predecessor of serious disease in some patients and is termed pathologic proteinuria. In general, certain forms of glomerulonephritis, such as idiopathic membranous and focal sclerosing glomerulonephritis, may initially present with isolated asymptomatic proteinuria. After a period in which there are no other signs or symptoms of renal disease, proteinuria either increases to nephrotic levels or progressive renal failure begins.

Having spoken of this entity as isolated and asymptomatic proteinuria, we are presupposing that the patient has already had a careful clinical and laboratory evaluation which has not disclosed other significant nephrologic abnormalities. No further evaluation or treatment is indicated. Renal biopsy does not contribute importantly other than providing a more definitive prognosis. At the present time even those types of pathologic proteinuria which may initially present as asymptomatic proteinuria do not appear to be amenable to therapy.

Pyuria may be defined as the presence of more than four white blood cells per high-power field from a carefully collected urine specimen. It is usually attributable to infection in the GU tract; however, on rare occasion, it may occur in the absence of classical infection and without other abnormalities in the urinalysis. In these circumstances pyuria deserves special consideration. Tuberculous infection of the GU tract, as well as infection with fungi, should be considered. Nephritis associated with systemic lupus erythematosus is a recognized cause of a urinalysis which contains abnormal numbers of white blood cells in the absence of other signs and symptoms of renal disease. Rejection of the transplanted kidney and other forms of interstitial nephritis may also on occasion present initially with asymptomatic isolated pyuria.

Evaluation of asymptomatic pyuria should be undertaken when it is demonstrated in repeated urinalyses from carefully collected urine samples. Cultures for tuberculosis are indicated and intravenous pyelography may be useful in demonstrating the characteristic lesions of GU tract tuberculosis. In the immunosuppressed patient or in the patient with recognized systemic fungal diseases, special cultures for fungi should also be done. A careful clinical and laboratory search for evidence of systemic lupus erythematosus should be carried out and agents such as antibiotics and diuretics, which may potentially produce an interstitial nephritis, discontinued. Treatment, of course, is dictated by the specific diagnosis.

TABLE 2
The Most Frequent Causes of Asymptomatic Hematuria

Urinary tract infection
Stones
Prostatic disease
Tumors:
25% incidence with gross hematuria
2% incidence with microscopic hematuria
Glomerulonephritis
Interstitial nephritis
Cystic kidney disease
Papillary necrosis
Tuberculosis
Hemorrhagic states
Vascular malformations

Hematuria is the most troublesome and potentially serious problem when it is encountered as an isolated finding in the asymptomatic patient. Abnormal numbers of red blood cells may enter the urine anywhere in the kidney or urinary tract, and may be caused by such diverse lesions as glomerulonephritis, benign and malignant masses, cysts, infection, and hemorrhagic states.[4,5] The most frequent causes of asymptomatic hematuria are presented in Table 2. The incidence of each of these entities varies considerably with the age, sex, and racial background of the patient. Although there is a significant incidence of neoplastic lesions with microscopic hematuria, a tumor etiology is even more likely in the presence of gross hematuria.

Evaluation of asymptomatic hematuria should begin with a review of some aspects of the patient's history. The patient should be questioned about the timing of the hematuria. When it occurs upon initiation of voiding, an anterior urethral bleeding site is suggested. When hematuria is only evident at the termination of voiding, a site near the posterior urethra, bladder neck, or trigone is more likely. Hematuria equally present throughout urination usually has a source above the level of the bladder. Recurrent episodes of either gross or microscopic hematuria, in association with upper respiratory tract illnesses, immunization, or exercise, suggest glomerulonephritis. Symptoms of stone disease and infection should be sought. Polycystic kidney disease and sickle cell disease frequently produce hematuria and may be suggested from a careful review of the patient's family history. Unusual bleeding other than in the GU tract, as well as the use of anticoagulant medications, may lead one to suspect an underlying coagulopathy.

Careful performance of the urinalysis by the responsible physician is also important. As noted above, when microscopic hematuria is accompanied by qualitatively detectable albuminuria, a glomerular origin is likely. Red blood cell casts can only form within the tubules of the kidney and indicate a renal origin for hematuria. Early morning urine, as well as urine obtained after exercise, should be examined since red cell casts may be more prevalent under these circumstances.

As outlined in Table 3, special studies may be required in the evaluation of hematuria. An intravenous pyelogram should be obtained in most cases; it is especially useful for demonstrating mass lesions in the GU tract, as well as stones and papillary necrosis. Cysts may be further evaluated with sonography if there is any question as to malignancy; absence of internal echoes means that a cyst is probably benign. Cyst puncture under sonographic control allows aspiration of fluid for cytological study, as well as instillation of contrast media. Demonstration of an irregular cyst wall strongly suggests a renal cell carcinoma.

When no cause for hematuria is apparent from the intravenous pyelogram, or when a lesion requires further definition, cystoscopy should be carried out. This may permit direct visualization of bleeding sites and, with great care, may allow sampling of urine from individual ureters. Additionally, retrograde pyelography may disclose lesions not demonstrable by an intravenous pyelogram.

In cases in which cystoscopy, as well as intravenous pyelography, fails to disclose a source for hematuria, renal arteriography should be considered. In this way masses too small to demonstrate by the

TABLE 3
Special Studies for Asymptomatic Hematuria

1. INTRAVENOUS PYELOGRAM	tumors, cystic disease, stones, papillary necrosis.
2. SONOGRAM	simple cyst vs tumor.
3. CYSTOSCOPY (RETROGRADE PYELOGRAPHY)	lower GU tract lesions, evaluation of ureteral urine.
4. RENAL ARTERIOGRAPHY	cyst vs tumor, occult tumors, vascular malformations.
5. RENAL BIOPSY	glomerulonephritis, interstitial nephritis.

previous techniques may be localized. Additionally, vascular malformations leading to hematuria may be demonstrable only with arteriography. When arteriography does not disclose an abnormality and when no bleeding is found from the lower urinary tract by cystoscopy, hematuria is probably caused by interstitial renal disease or glomerulonephritis. Interstitial nephritis may result from commonly used drugs such as diuretics and antibiotics. Such agents should be discontinued and the patient followed closely to determine whether the hematuria resolves. Glomerular lesions are probably the most frequent cause of isolated hematuria of renal origin in the asymptomatic patient who has no lesion demonstrable by pyelography or arteriography. In general, glomerular lesions which produce only hematuria and are not associated with other systemic abnormalities have an excellent prognosis. They may occur at any age but are more frequent in children and young adults. However, other more severe forms of glomerulonephritis may occasionally present with asymptomatic isolated hematuria. Such disease processes include hereditary glomerulopathies, collagen vascular disease, and unresolved poststreptococcal glomerulonephritis. Thus, a diligent search for nonrenal signs and symptoms of these diseases, as well as appropriate laboratory tests, should be carried out.

In the patient with hematuria of renal origin and normal renal arteriography, it may be important to establish a definitive diagnosis by renal biopsy. If this is not done, hematuria may recur or persist, and physicians caring for these patients in the future may be concerned over neoplastic lesions which might have been missed in previous investigations. Frequently these concerns lead to multiple, unnecessary arteriographic and cystoscopic procedures. Percutaneous renal biopsy in most such patients will provide a definitive diagnosis and thus obviate further invasive diagnostic procedures. Additionally, the biopsy may be useful in providing prognostic data on the potential severity of the glomerular lesion.

As can be seen from the above discussion, evaluation of an abnormal urinalysis from an otherwise healthy individual involves consideration of a large number of potential diagnoses. If the meaning of individual abnormalities in the urinalysis is not carefully considered, valuable time may be wasted and inappropriate and expensive procedures may be performed. The general principles discussed above, however, allow for a rational and effective approach to this problem.

REFERENCES

1. LIPPMAN RW: *Urine and the Urinary Sediment.* Springfield, Charles C Thomas Publisher, 1973.

2. BLACK DAK: Diagnosis in renal disease, in Black DAK (ed): *Renal Disease,* 3 ed. Oxford, Blackwell Scientific Publications Ltd, 1972, pp 827–840.

3. NORTHWAY JD: Hematuria in children. *J Pediatr* 78:381–396, 1971.

4. HENDLER E, KASHGARIAN M, HAYSLETT J: Clinicopathologic correlation of primary hematuria. *Lancet* 1:458–463, 1972.

5. COE FL: The clinical and laboratory assessment of the patient with renal disease, in Brenner BM, Rector F (eds): *The Kidney.* Philadelphia, WB Saunders Company, 1976, pp 765–805.