The Investigation of Hematuria

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Persistent microscopic hematuria is present in about 6% of the population, but probably only a small minority have hematuria that does not originate from the glomerulus. Careful analysis of phase-contrast urine microscopy by a skilled observer is critically important in the investigation of hematuria. In glomerular disease, urine microscopy often is second only to renal biopsy examination in helping make a diagnosis. Glomerular and nonglomerular hematuria are distinguished easily on phase-contrast urine microscopy or by an automated peripheral blood cell counter. However, urine microscopy provides additional information about casts and other features that may enable such disparate diagnoses as Fabry's disease, sickle cell disease, and cystine calculi to be made. Macroscopic nonglomerular hematuria is of particular significance because it is much more likely than microscopic hematuria to be associated with malignancy. Macroscopic hematuria originating from the glomerulus indicates the presence of crescentic disease, which requires urgent assessment by renal biopsy examination. We advocate a renal biopsy examination in any individual with a persisting urinary erythrocyte count greater than 100,000/mL. Thirty percent of patients with isolated microscopic hematuria have mesangial immunoglobulin A glomerulonephritis (IgAN) shown on biopsy examination and 20% to 40% of these patients will progress to renal failure without treatment.
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The importance of careful evaluation of hematuria cannot be overstated. This is the commonest urinary abnormality and often reflects serious underlying renal and urinary tract disease. Urine microscopy, the simplest and cheapest of all investigations, can provide a wealth of information about the diagnosis, prognosis, and, indeed, even the likely treatment requirements in renal disease, but it is essential that evaluation is by phase-contrast microscopy and that it is performed by the nephrologist or a scientist with special expertise in the area.

The current emphasis on global prevention of renal failure[1] has revived some interest in the importance of hematuria, which is beginning to take its rightful place alongside proteinuria in population screening studies seeking early renal disease.[2]

Urinary microscopy by a skilled observer comes closer than any other test to providing a presumptive diagnosis in glomerular disease, which is by far the commonest cause of hematuria. This can be delineated more clearly only by renal biopsy examination, an invasive test that currently is underused in patients with isolated hematuria.

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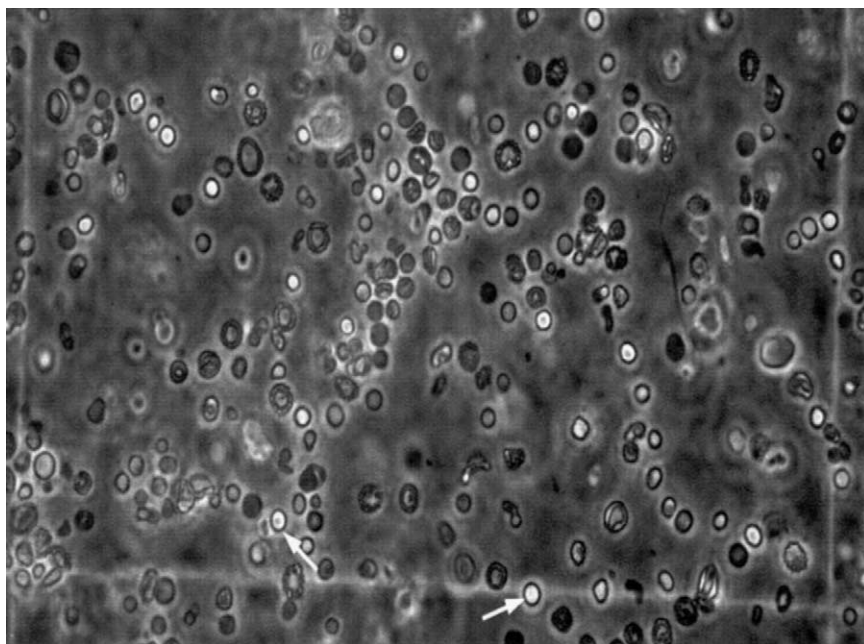
Prevalence

Microscopic hematuria is the most frequent reason for referral of a patient to a nephrologist in our experience.

Studies show great variation in the prevalence of microscopic hematuria from as low as .18% to as high as 16.1%.[3] When screening for hematuria using phase-contrast urine microscopy, a group of skilled observers in Melbourne found a prevalence of 6%.[4] The recent AusDiab (Australian Diabetes, Obesity and Lifestyle) Study in Australia that used dipstick screening identified hematuria in 4.6% of 11,247 subjects.[2] Perhaps the recent disenchantment of some urologists[5] with the value of testing for microscopic hematuria reflects our observation that very few (.15%) of our 6% of patients with hematuria had nonglomerular bleeding from calculi, tumors, and other conditions of urologic interest.

Glomerular and Nonglomerular Hematuria

The description of glomerular and nonglomerular erythrocytes in the urine 25 years ago[6] completely revolutionized our approach to the investigation of hematuria. The validity of differences between glomerular and nonglomerular erythrocytes and their clinical significance has been confirmed in a number of subsequent studies. Some

Figure 1 Typical appearance of erythrocytes in glomerular hematuria in which cells are small and vary in size, shape, and hemoglobin content.

of these have compared phase-contrast microscopy with automated methods that measure erythrocyte size, shape, and hemoglobin pigmentation to distinguish the 2 types of cells.[7-21] The value of the distinction between glomerular and nonglomerular erythrocytes as a guide to investigation is now well accepted (Figs 1 and 2).[3]

The differences are so obvious using phase-contrast microscopy that it is surprising this observation was made as recently as 1979.[6] Addis[22] in 1950 referred to pale cells lacking hemoglobin pigment in glomerulonephritis but did not further delineate the important differences. This loss of hemoglobin pigment occurs rapidly in acid urine and is seen quite often in nonglomerular hematuria.

The Different Characteristics of Glomerular and Nonglomerular Hematuria

1. Glomerular erythrocytes are smaller than nonglomerular erythrocytes (Figs 1 and 2) and the diagnosis can be made by a Coulter counter (Fig 3).
2. The smaller glomerular erythrocytes vary greatly in both shape and size whereas nonglomerular erythrocytes are uniform in size and shape.
3. Glomerular erythrocytes usually have lost a large amount of their hemoglobin pigment and are pale.

Figure 2 Typical nonglomerular erythrocytes that are uniform in size and shape but show 2 populations of cells because a small number have lost their hemoglobin pigment.
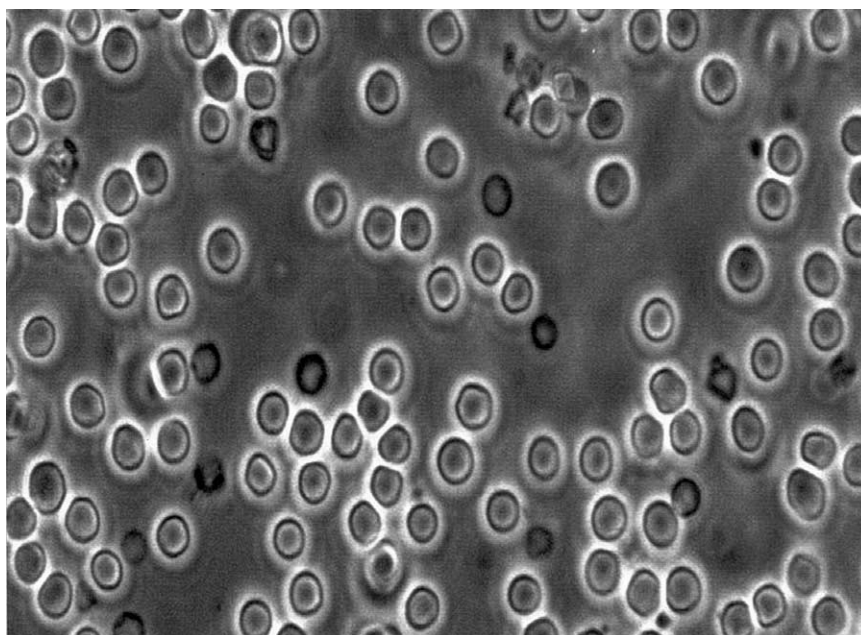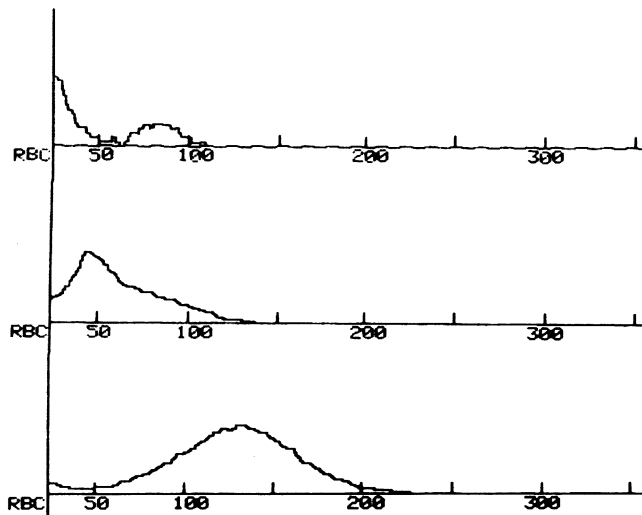
Figure 3 Distribution of erythrocyte volumes in samples of urine sediment after analysis in a Coulter counter. Top line, bimodal volume distribution in glomerular bleeding. Middle line, modal volume distribution <50 fL indicates glomerular bleeding. Bottom line, modal volume distribution >100 fL indicates nonglomerular bleeding.

Nonglomerular erythrocytes, although uniform in size and shape, may show variation in hemoglobin pigment. They frequently are well hemoglobinized but, particularly in an acid urine, will have lost some or all of their pigment. Based on the amount of hemoglobin, there may appear to be 2 or occasionally 3 populations of cells in nonglomerular hematuria.

4. Erythrophagocytes (Fig 4) commonly accompany glomerular hematuria. Their presence confirms the hematuria is glomerular in origin. Erythrophagocytes are renal tubular cells that have ingested erythrocytes in the tubule.[23]

5. The appearance of erythrocyte changes and cast numbers are altered by a low specific gravity or after a diuresis. Casts do not form in dilute urine and a concentrated urine (ie, not collected during a diuresis) should be used for urine microscopy.

The Significance of Casts

Glomerular erythrocytes always are accompanied by abnormal casts, provided the specific gravity of the urine is greater than 1.010 and the urine is examined shortly after collection. Casts also may be preserved by the addition of formalin to the urine. The most significant casts are those containing erythrocytes (Fig 5). The number of erythrocyte casts correlates strongly with the number of crescents on biopsy examination (Fig 6). A high erythrocyte count (>500,000/mL) accompanied by erythrocyte casts indicates the presence of glomerular crescents[24] and that a renal biopsy examination is needed urgently.

A very thin hyaline cast containing erythrocytes, which we have labeled a string cast (Fig 7), may be associated with glomerular bleeding, particularly in the more benign context of thin basement membrane nephropathy (TBMN).[23]

In renal disease, large, elongated, and convoluted hyaline casts, granular casts, cellular casts, and casts containing fat or crystals may accompany the hematuria.

Normal urine contains 50 to 250 hyaline casts/mL depending on its concentration. The cast counts may increase to very high numbers (median, 14,000/mL) in normal individuals after a long-distance run, and abnormal casts including granular, cellular, and erythrocyte casts[25] may appear transiently.
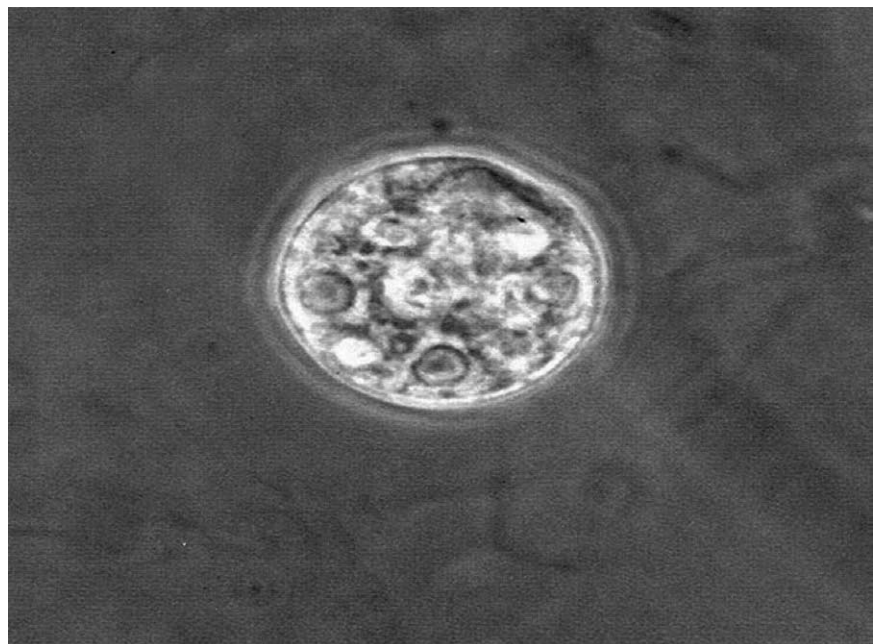

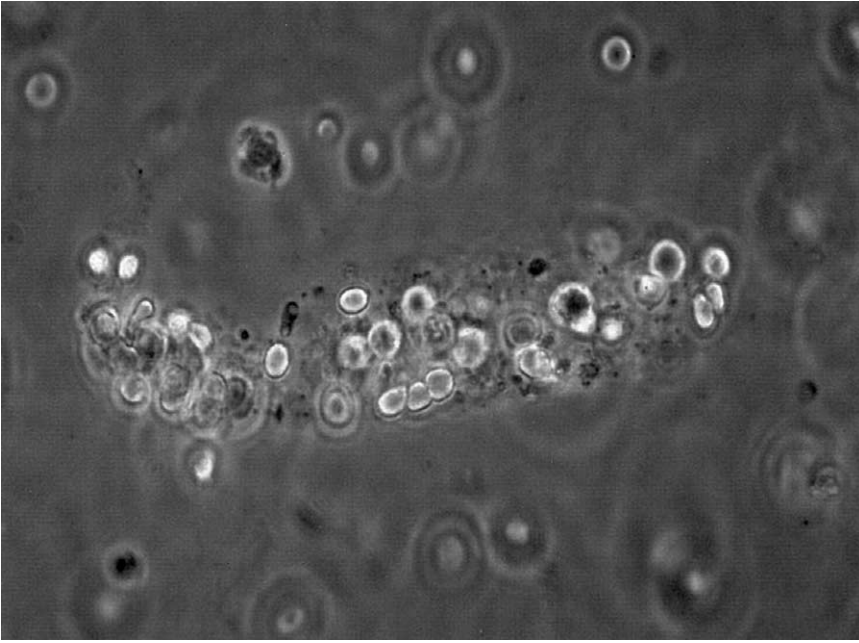**Figure 4** An erythrophagocyte indicating glomerular bleeding.

Figure 5 A cast containing numerous erythrocytes—a sign of an active glomerular lesion.

The Investigation of Hematuria

The major clinical impact of being able to distinguish glomerular and nonglomerular erythrocytes has been to simplify the investigation of hematuria greatly.

A patient in whom glomerular hematuria has been identified requires careful quantitative evaluation of cells and casts by phase-contrast urine microscopy. The number of glomerular erythrocytes correlates strongly with the activity of the underlying lesion and specifically with the number of crescents found on biopsy examination.[24] Microscopy occasionally provides a definitive diagnosis as in Fabry's (Fig 8) or sickle cell disease.[26] Renal function tests, quantification of urine protein, and a renal ultrasound all should be performed. The most informative investigation is a renal biopsy examination and assessment of the need for renal biopsy examination in microscopic hematuria is considered separately.

A patient in whom nonglomerular hematuria has been identified also requires careful urine microscopy, which may lead to a specific diagnosis such as urinary tract infection, triple phosphate, or cystine calculi. A cystoscopy should be undertaken and ureteroscopy and ureterorenoscopy now are performed frequently.[27] Various modes of imaging such as computed tomography scanning, ultrasound, or even angiography may be required in addition to cystoscopy. The major focus in reaching a definitive diagnosis is the treatment of the underlying cause and in particular the diagnosis or exclusion of malignancy. Newer forms of computed tomography scanning have been developed to identify causes of nonglomerular hematuria.[28]

URINARY RED CELL COUNTS and % OF BIOPSIES WITH CRESCENTS
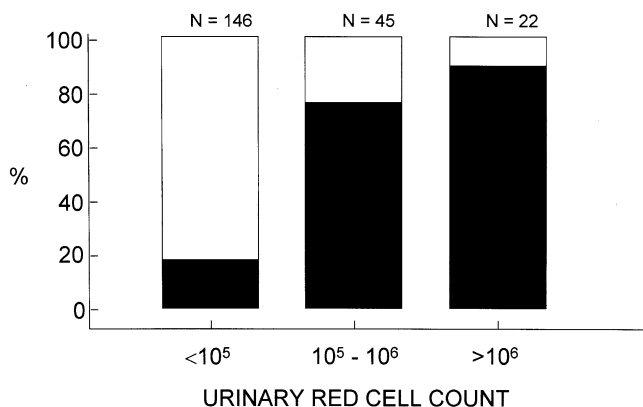

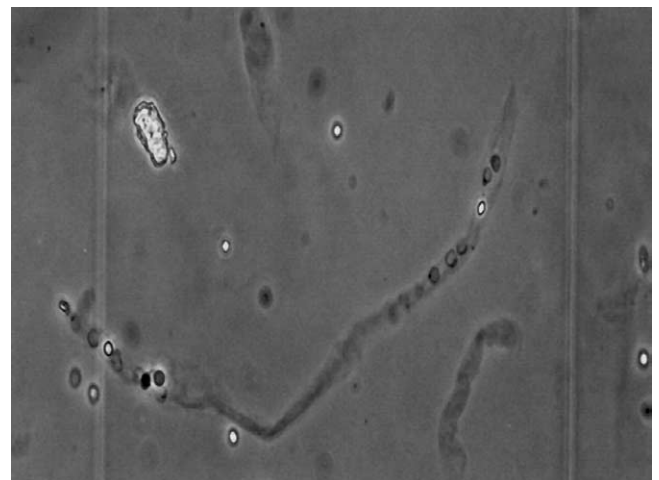**Figure 6** Urinary erythrocyte count versus percent of biopsy specimens with crescents.

Figure 7 A string cast. A thin hyaline cast containing erythrocytes commonly present in TBMN.

Figure 8 Left, A characteristic irregularly shaped myelin body. This resembles a fat droplet but is enclosed in an irregular envelope. *On the right,* The myelin body seen on the left shows 'Maltese cross' birefringence with polarized light. The envelope is seen extending from the left of the Maltese cross. This is a diagnostic finding in Fabry's disease. Cholesterol droplets show a similar appearance but lack the envelope typically seen in Fabry's disease.
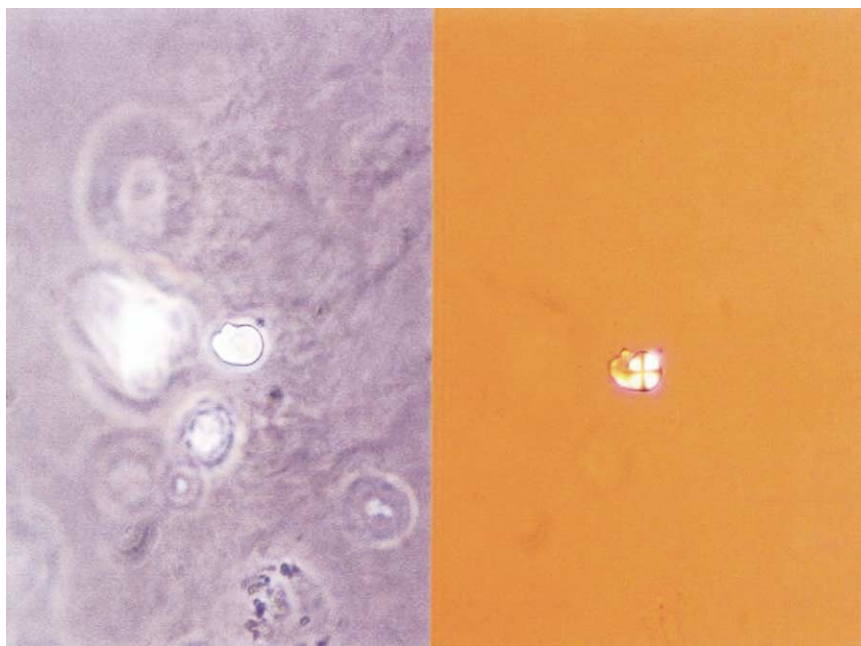
Before the recognition of glomerular and nonglomerular hematuria, most patients with glomerular hematuria were subjected to many of the tests used to investigate nonglomerular hematuria including cystoscopy before being reassured that the bleeding did not indicate a tumor. Because persistent microscopic hematuria is 40 times as frequent as persistent nonglomerular hematuria, only a very small percentage of all cases of microscopic hematuria[5] are likely to show a lesion on cystoscopy. Despite this, the current advice of the American Urological Association is that all patients over 40 years of age with hematuria should undergo cystoscopy.[3] Malmstrom,[5] in contrast, suggests it is time to abandon testing for microscopic hematuria, which is a recommendation based on the rarity of urologic lesions in patients with microscopic hematuria. Such a policy would be highly detrimental to the proper practice of clinical nephrology, particularly with the current emphasis on early detection of renal disease and interventions to retard the progression to renal failure.[1,2]

Causes of Hematuria

The causes of hematuria are shown in Table 1. Although glomerular disease is the major cause of glomerular hematuria, this also occurs in normal subjects after exercise and in patients with bleeding diatheses, on anticoagulants, or taking other drugs. Medications that cause interstitial nephritis often result in glomerular hematuria, and those that cause crystalluria (such as sulfonamides) or hemorrhagic cystitis[30] may result in nonglomerular hematuria.

Macroscopic Hematuria and Microscopic Hematuria

Many causes of glomerular hematuria and almost all causes of nonglomerular hematuria can manifest as either microscopic or macroscopic hematuria (Table 1).

Malignant tumors are more likely to be detected in patients with nonglomerular macroscopic hematuria than in those with microscopic hematuria.[5]

Macroscopic hematuria also has particular significance when the hematuria originates from the glomerulus because this almost always indicates crescentic disease. We have correlated the level of hematuria and the occurrence of crescents in a very large series of patients with IgA glomerulonephritis (IgAN).[24] The same correlation is found in lupus and other active forms of glomerulonephritis.[31] The inflammatory process in glomeruli that leads to crescent formation in IgAN[32] is accompanied by inflammatory markers that can be detected in the urine. These show marked differences between IgAN and TBMN.[33] In contrast to the inflammatory process that causes hematuria in IgAN, in TBMN the erythrocytes escape through gaps in the thin basement membrane and hematuria does not reflect inflammation or the likelihood of glomerular loss.

The ominous prognostic significance and fulminating course in diseases such as Wegener's granulomatosis, Goodpasture's syndrome, and microscopic polyangiitis makes the recognition of the significance of macroscopic hematuria particularly important in this group. Because of the rapidity with which the crescents develop and progress in these cases, we regard macroscopic glomerular hematuria as a medical emergency requiring urgent renal biopsy diagnosis and treatment.

Table 1 Causes of Hematuria

Diagnosis	Comments	Macroscopic
Glomerular hematuria		
Glomerular lesions		
Thin basement membrane nephropathy	53% of cases presenting in Melbourne[4]	Very rare
Mesangial IgA glomerulonephritis	30% of cases presenting in Melbourne[4]	Common under age 35 and in men
Focal and segmental hyalinosis and sclerosis (focal glomerulosclerosis)		0
Lupus glomerulonephritis		Rare
Crescentic glomerulonephritis including Wegener's granulomatosis, microscopic polyangiitis, and Goodpasture's syndrome		+++
Membranous glomerulonephritis		Rare
Mesangiocapillary glomerulonephritis	Rare in Melbourne	+
Dense deposit disease	Rare in Melbourne	+
Post-streptococcal glomerulonephritis	Rare in Melbourne	+++
Nonglomerular disease		
Autosomal-dominant polycystic kidney disease	Also may be nonglomerular	++
Exercise hematuria[25]	Also may be nonglomerular	+
Bleeding diathesis	Also may be nonglomerular	+
Drugs including anticoagulants	Also may be nonglomerular	+
Nonglomerular hematuria		
Urinary tract infection		+++
Urinary tract calculi		++
Hypercalciuria and hyperuricosuria		Rare
Autosomal-dominant polycystic kidney disease		+
Benign prostatic hypertrophy		++
Transitional cell carcinoma		++
Renal cell carcinoma		++
Prostatic carcinoma		+
Exercise hematuria		+
Trauma		+
Bleeding diathesis and anticoagulants	17% have an underlying cause and bleeding is precipitated by anticoagulant	+
Drugs	Crystalluria and hemorrhagic cystitis	+
Renal papillary necrosis		+
Sickle cell disease		++
Unknown whether glomerular or nonglomerular		
Hematuria after percutaneous coronary artery angioplasty[29]		

NOTE. The causes of hematuria are listed in order of frequency as far as this can be ascertained. +, sometimes; ++, common; +++, very common.

Such patients then may have a good long-term outcome despite crescents in 80% or more glomeruli in the acute phase of their illness.

Crescents accompanied by high urinary erythrocyte counts may appear during pregnancy in conditions in which they usually are not found such as membranous glomerulonephritis.[34]

Macroscopic hematuria may cause renal failure because of acute tubular necrosis in glomerular diseases. We first documented this in mesangial IgAN,[35] and it recently was described in TBMN[36] and in paroxysmal hemoglobinuria.[37] The latter finding suggests hemoglobin pigment may contribute to the renal failure in IgAN and TBMN.

Indications for Renal Biopsy Examination in Hematuria

In a series of consecutive patients presenting with isolated microscopic hematuria in Melbourne, renal biopsy specimens showed 50% had TBMN and 30% had mesangial IgAN.[4] The remainder had other glomerular diseases including lupus glomerulonephritis, dense deposit disease, and mesangiocapillary glomerulonephritis. In all of these conditions except TBMN, a high urinary erythrocyte count has powerful prognostic significance.[31,38,39]

It is cases with isolated microscopic hematuria without proteinuria in which the greatest controversy exists about

Table 2 Distinguishing Features on Urine Microscopy of TBMN and IgAN

TBMN	IgAGN
Erythrocyte count	
Generally constant 30,000–800,000/mL; decreases in late pregnancy	Varying 13,000–200,000/mL with occasional peaks greater than 1,000,000; count may decrease to normal in remission and with treatment; count often increases in late pregnancy
Casts	
About 250–500/mL, except when associated with proteinuria >.5 g	≥1,000–2,000/mL except in remission when cast count may be normal
Characteristically thin hyaline casts; thin hyaline casts or string casts (Fig 6) that contain erythrocytes	Casts characteristically larger, longer, and fatter than in TBMN include hyaline and granular casts, casts containing cells and fat particles, and erythrocyte and hemoglobin casts; urine deposit is much more abnormal than in TBMN
With associated vesico-ureteric reflux, large hyaline, granular and convoluted casts may occur in small numbers	Erythrocyte casts and hemoglobin levels increase in number as the erythrocyte count increases in crescentic disease
Macroscopic hematuria very rare	Macroscopic hematuria indicates crescents; more common under age 35 and in men[38]

NOTE. We find a common association between TBMN and reflux nephropathy. In addition to being associated with more casts and proteinuria, this group appears to have a worse prognosis than those with TBMN.

the value of renal biopsy examination. A continuing high urinary erythrocyte count (>100,000/mL) carries the strongest relative risk (4.3) of deterioration in renal function in IgAN.[38] Based on this observation, it has been our policy to perform biopsy examinations in individuals with isolated microscopic hematuria with persistent counts greater than 100,000/mL unless there is clear evidence of a family member with hematuria and benign features on their urine microscopy that suggest TBMN (Table 2). Knowing that IgAN is the commonest form of glomerulonephritis world-wide and the commonest biopsy examination–proven glomerulonephritis to cause kidney failure in Australia provides a powerful argument for a renal biopsy examination to establish an early diagnosis. IgAN is responsible for 20% to 40% of all cases of end-stage renal failure, but evidence from controlled trials confirms the value of specific treatment in IgA glomerulonephritis[40] to retard disease progression.

We would perform a renal biopsy examination when microscopic hematuria is accompanied by proteinuria levels greater than .5 g/24 hours. Proteinuria is a major risk factor for deterioration in most glomerular diseases including TBMN. Renal biopsy specimens in patients with TBMN and proteinuria show interstitial scarring and glomerular lesions of segmental focal and segmental hyalinosis and sclerosis. We believe these patients have associated reflux nephropathy reflected by typical histologic changes and by lateral displacement of ureteric orifices. The small number of cases of TBMN in which renal function had deteriorated occurred in this group with glomerular and interstitial sclerosis consistent with reflux nephropathy.

A policy of frequent renal biopsy examinations in isolated microscopic hematuria requires careful attention to minimize any risks.[41]

Hematuria and the Diagnosis of Other Forms of Glomerular Disease

Focal and Segmental Hyalinosis and Sclerosis (Focal Sclerosis)

The secondary form of focal and segmental hyalinosis and sclerosis is probably the commonest form of glomerular pathology. The primary form presents as the nephrotic syndrome and may have associated microscopic hematuria. The secondary form first documented in reflux nephropathy[42] occurs as a secondary lesion in most progressive glomerular and tubular interstitial diseases.[43] This lesion resembles that seen in the remnant kidney model in animals and is the current focus of treatment to prevent progression by control of proteinuria.[1] The urinary erythrocyte count in focal and segmental hyalinosis and sclerosis is about 20,000 to 50,000/mL and is accompanied by 1,000 to 5,000 casts/mL (including abnormal hyaline, granular, and cellular casts), usually together with oval fat bodies and fat particles in casts.

Membranous Glomerulonephritis

This is the commonest cause of the nephrotic syndrome in our experience. The urinary erythrocyte count usually varies from 30,000 to 60,000/mL but may in rare cases exceed 100,000/mL. The count returns to normal after treatment. Oval fat bodies and casts containing fat and oval fat bodies are prominent.

Lupus Glomerulonephritis

In active disease with proliferative lesions, the erythrocyte count may be greater than 100,000/mL but crescents occur in lupus glomerulonephritis with counts less than 100,000/

mL.[31] We always perform a biopsy examination if microscopic hematuria greater than 50,000 erythrocytes/mL is accompanied by positive serologic tests for lupus. Active lesions can occur in the absence of proteinuria.

Crescentic Glomerulonephritis, Wegener's granulomatosis, Goodpasture's Syndrome, and Microscopic Polyangiitis

Hematuria often is macroscopic or the urinary erythrocyte count is very high ($>10^6$/mL). Erythrocyte casts may be numerous. Both hematuria and casts disappear with successful treatment and the long-term course may be excellent with early treatment. The urine deposit may appear normal and contain no proteinuria 25 years later despite crescents in 80% to 90% of glomeruli in the acute phase.

Conclusions

Hematuria is a very important feature in renal and urologic disease. Screening for microscopic hematuria is now being undertaken, in addition to screening for proteinuria, in an attempt to detect and treat early kidney disease to prevent progression to renal failure.

All patients with hematuria must be investigated. Phase-contrast urine microscopy performed carefully by an expert is an invaluable test in the evaluation of hematuria. A specific diagnosis should be sought. Urine microscopy as a single test can provide a diagnosis in such disparate conditions such as hyperuricosuria, Fabry's disease, cystine, and infection stone disease, and in sickle cell disease.

Urine microscopy reflects the glomerular pathology and only a renal biopsy examination provides more specific information when there is an underlying glomerular disease. A high urinary erythrocyte count, particularly when accompanied by erythrocyte casts, indicates active inflammation and often crescents, and requires prompt diagnosis and treatment.

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