Glomerular Hematuria and the Utility of Urine Microscopy: A Review


Evaluation of hematuria and microscopic examination of urine sediment are commonly used tools by nephrologists in their assessment of glomerular diseases. Certain morphological aspects of urine red blood cells (RBCs) seen by microscopy may help in identifying the source of hematuria as glomerular or not. Recognized signs of glomerular injury are RBC casts or dysmorphic RBCs, in particular acanthocytes (ring-shaped RBCs with protruding blebs). Despite being a highly operator-dependent test, urine sediment examination revealing these signs of glomerular hematuria has demonstrated specificities and positive predictive values ranging between 90%-100% for diagnosing glomerular disease, although sensitivity can be quite variable. Hematuria is a commonly used tool for diagnosing patients with proliferative glomerulonephritis such as IgA nephropathy, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, and lupus nephritis, sometimes even as a surrogate for kidney involvement. Studies examining the role for hematuria in monitoring and predicting adverse outcomes in these diseases have shown inconsistent results, possibly due to inconsistent definitions that often fail to consider specific markers of glomerular hematuria such as dysmorphic RBCs, acanthocytes, or RBC casts. A consensus definition of what constitutes glomerular hematuria would help standardize use in future studies and likely improve the diagnostic and prognostic value of hematuria as a marker of glomerulonephritis.

Introduction

Glomerular diseases, particularly those characterized as “nephritic,” are associated with hematuria. Hematuria is defined by an “abnormally high number” of urinary red blood cells (RBCs), often quantified ≥3 RBCs per high-power field (HPF). Microscopic hematuria may be incidentally detected on routine urinalysis and can be characterized further as isolated, intermittent, or persistent. Isolated hematuria may occur after exercise or prolonged recumbency, while pathological lesions in the kidney or urinary tract are likely to cause intermittent or persistent hematuria. Hematuria may be classified based on its origin: glomerular versus urologic. We focus on glomerular hematuria with respect to its pathogenesis, evaluation, and utility in diagnosis and management of several disease states.

Dysmorphic RBCs as a Marker for Glomerular Pathology

The shape of RBCs in urine may differ depending on their origin. Although not mutually exclusive, RBCs originating from the urinary tract are usually isomorphic—that is, similar in appearance to circulatory ones—whereas those traversing through glomeruli and tubules may have a variety of morphological alterations termed dysmorphic RBCs. In patients with hematuria, the presence of dysmorphic RBCs and RBC casts may suggest underlying glomerular pathology. There is no uniform definition of dysmorphic erythrocyturia; various shapes including acanthocytes (ringed shape with blebs), stomatocytes (central pale groove), and echinocytes (surface spicules) among others are considered dysmorphic. In 1982, Fairley and Birch examined the shapes of urine RBCs from 58 patients with biopsy-proven glomerular disease as compared with 30 patients with urological hematuria. Various shapes of dysmorphic RBCs were seen in 55 of 58 individuals (95%) with glomerular disease, but none were found in the patients with urological disease in whom the RBCs were nearly all isomorphic concave discs. The possible shapes of dysmorphic RBCs were further characterized by Köhler et al in 1991. They demonstrated that of all possible dysmorphic forms of RBCs, acanthocytes were the RBCs that best identified glomerular hematuria; other forms—such as echinocytes, stomatocytes, and schizocytes—were found in both glomerular and nonglomerular hematuria. Since then, acanthocytes have been recognized as the most characteristic dysmorphic RBCs suggesting glomerular hematuria (Fig 1).

Many additional studies have examined the diagnostic performance of urinary microscopic abnormalities to differentiate between glomerular and nonglomerular hematuria. Various definitions and cutoffs of dysmorphic RBCs have been explored (Table 1). Studies focus on the percentage of urinary acanthocytes or dysmorphic RBCs among total RBCs to define glomerular hematuria. These studies have a demonstrated sensitivity that is variable and often poor, as would be expected because finding urine abnormalities depends on the experience and patience of the observer. When correctly identified, the presence of dysmorphic RBCs and acanthocytes provides high specificity and positive predictive value (90%-100%) for glomerular disease. The presence of RBC casts also suggests glomerular disease with high specificity of 97% but low sensitivity (Table 1). Dysmorphic RBCs and RBC casts are
therefore useful markers of glomerular disease, but they are not definitive. The less stringent the cutoff percentage of acanthocytes or dysmorphic RBCs to define glomerular disease, the lower the specificity, which suggests that such RBC changes may occur in small amounts even without the presence of overt glomerular disease. RBC casts have been demonstrated in patients with interstitial nephritis or after exercise. Dysmorphic RBCs and RBC casts provide strong, but not definitive, evidence for glomerular hematuria.

**Method of Urine Microscopy Assessment**

Analysis of freshly collected urine by dipstick followed by microscopy is the most common clinical method for detecting hematuria. The preferred method of collection of urine is to use the second morning void specimen because it may contain the most acanthocytes, though controlled data are lacking. In clinical practice, a random urine specimen collected at any time of day is used. Urine should be stored at 4°C if not analyzed within an hour of collection.

For microscopy, ideally 10 mL of urine is centrifuged for 5 minutes at a relative centrifugal field of 400-500g; then 9.5 mL of the supernatant is discarded, and the remaining 0.5 mL with pellet is resuspended by pipetting, thus concentrating the sediment 20-fold. Dysmorphic RBCs have a lower hemoglobin content than isomorphic RBCs and thus a lower specific gravity. Centrifugation at 500g compared with 400g may improve the recovery ratio of dysmorphic erythrocytes. Light microscopy (including phase contrast microscopy), automated blood cell counting, and automated urine flow cytometry are methods for evaluating urine sediment. Wright’s stain can distinguish hypochromic, dysmorphic RBCs from normochromic, biconcave, isomorphic RBCs. Phase

**Figure 1.** Urine sediment microscopy photograph. Bright-field microscopy with lowering of the condenser to increase contrast, showing an erythrocyte cast (upper left panel) and acanthocytes with characteristic protruding blebs (upper right panel). Acanthocyte seen on phase contrast microscopy (bottom 2 panels). Original magnification, ×40.
contrast microscopy is regarded as the best method for assessing acanthocytes due to its better ability to identify RBC dysmorphism compared with conventional bright-field microscopy. In the absence of a phase contrast microscope or when the individual analyzing the urine sample is unfamiliar with this instrument, bright-field microscopy can be used as an alternative.

### Table 1. Sensitivity and Specificity of Different Definitions of Abnormal Urine Microscopic Examination Findings for the Diagnosis of Glomerular Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Gold Standard Outcome; Method of Microscopy Assessment</th>
<th>Urine Measure</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamadah et al</td>
<td>482 patients with urinalysis and microscopy before kidney biopsy</td>
<td>Biopsy-proven glomerular disease; microscopy performed by lab tech</td>
<td>Dsymorphic RBCs ≥ 25%</td>
<td>20.4%</td>
<td>96.3%</td>
<td>94.6%</td>
</tr>
<tr>
<td>Martinez et al</td>
<td>65 patients with nephrolithiasis vs 66 with biopsy-proven GN (patients divided into derivation and validation cohorts)</td>
<td>Biopsy-proven GN; unknown if microscopy performed by lab tech or nephrologian</td>
<td>Dsymorphic RBCs ≥ 22%</td>
<td>Derivation 90%</td>
<td>88%</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Validation</td>
<td>78%</td>
<td>84%</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acanthocytes ≥ 6% Validation</td>
<td>85%</td>
<td>82%</td>
<td>85%</td>
</tr>
<tr>
<td>Ohsaki et al</td>
<td>20 urological vs 32 glomerular hematuria (biopsy-proven GN in 13 of 32)</td>
<td>Glomerular disease; microscopy performed by study authors</td>
<td>Acanthocytes ≥ 1%</td>
<td>87.5%</td>
<td>100%</td>
<td>NA</td>
</tr>
<tr>
<td>Crop et al</td>
<td>44 urological hematuria vs 24 definite GN diagnosis</td>
<td>Biopsy-proven GN; microscopy performed by lab tech</td>
<td>Dsymorphic RBCs ≥ 40%</td>
<td>21%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Ohisa et al</td>
<td>Hematuria in 250 nonglomerular vs 329 definite glomerular disease (biopsy proven in 284 of 329)</td>
<td>Diagnosis of glomerular disease; unknown if microscopy performed by lab tech or nephrologist</td>
<td>Dsymorphic RBCs &gt; 3%</td>
<td>83.3%</td>
<td>75.2%</td>
<td>NA</td>
</tr>
<tr>
<td>Heine et al</td>
<td>68 with clinical diagnosis of diabetic nephropathy vs 43 biopsy-proven GN</td>
<td>Biopsy-proven GN; unknown if microscopy performed by lab tech or nephrologian</td>
<td>Acanthocytes ≥ 5%</td>
<td>40%</td>
<td>97%</td>
<td>85%</td>
</tr>
<tr>
<td>Zaman et al</td>
<td>40 urological hematuria vs 42 GN (28 biopsy-proven)</td>
<td>Diagnosis of GN; microscopy performed by lab tech</td>
<td>Dsymorphic RBCs ≥ 10%</td>
<td>95%</td>
<td>24%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥20%</td>
<td>95%</td>
<td>34%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥50%</td>
<td>93%</td>
<td>43%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥90%</td>
<td>62%</td>
<td>85%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acanthocytes ≥ 1%</td>
<td>62%</td>
<td>89%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥2%</td>
<td>40%</td>
<td>95%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥5%</td>
<td>28%</td>
<td>95%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥10%</td>
<td>10%</td>
<td>98%</td>
<td>NA</td>
</tr>
<tr>
<td>Dinda et al</td>
<td>40 urological hematuria vs 82 GN</td>
<td>Biopsy-proven GN; unknown if microscopy performed by lab tech or nephrologian</td>
<td>Dsymorphic RBCs ≥ 20%</td>
<td>90%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acanthocytes ≥ 5%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Köhler et al</td>
<td>187 with urological or nonglomerular hematuria vs 147 with biopsy-proven GN</td>
<td>Biopsy-proven GN; unknown if microscopy performed by lab tech or nephrologian</td>
<td>Acanthocytes ≥ 5%</td>
<td>52%</td>
<td>98%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RBC casts</td>
<td>24.5%</td>
<td>97%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: GN, glomerulonephritis; lab tech, laboratory technician; NA, not applicable; PPV, positive predictive value; RBC, red blood cell.
Microscopy can be used with lowering of the condenser. Masked studies have demonstrated similar efficacy in identifying dysmorphic RBCs. One study found bright-field microscopy with lowering of the condenser and phase contrast microscopy (both at ×400 magnification) correlated well at detecting dysmorphic RBCs and acanthocytes (r = 0.88 and 0.90, respectively). This study used supravital staining with bright-field microscopy, which can provide better visualization of morphologic alterations. Another study showed similar high sensitivities and specificities of phase contrast and bright-field microscopy with lowering of the condenser, for identifying dysmorphic RBCs (both at ×400 magnification).14

Mechanisms of Dysmorphic RBCs

The average diameter of an erythrocyte is 6-8 μm, which is about 100 times the size of the endothelial fenestration (60-80 nm) in the glomerulus.16,17 The combination of glomerular capillary hydraulic pressure, glomerular basement membrane (GBM) integrity, and erythrocyte membrane deformability is required for its diapedesis through the GBM (Fig 2).18 Case reports have serendipitously captured RBC migration through the GBM in patients with normal GBM structure and with thin basement membranes.3,19,20 In immune-complex glomerulonephritis (GN), without cellular crescents, hematuria may result from small ruptures in GBM that may occur due to lysosomal digestion around deposited immune complexes.21 A similar process may occur in IgA nephropathy (IgAN) where deposits of IgA along the basement membrane lead to local destruction;21 however, GBM focal ultrastructural abnormalities such as thinning and lamination may be more important contributors to hematuria in IgAN. In a study of 415 IgAN kidney biopsy specimens, GBM lesions were identified in 48% of IgAN cases compared with 16% of control specimens that had mesangio proliferative GN without IgA deposits (P < 0.01); among cases of IgAN, GBM lesions were found in 80% of patients during severe hematuria (>50 RBC/HPF) compared with 33% of patients without hematuria (P < 0.01).15

 Passage of RBCs through a disrupted GBM might be sufficient for dysmorphism, but additional factors may contribute. Based on topo-optical studies, initial alteration of the RBC membrane occurs in the glomerulus—lysosomal exocytosis and inflammatory cells may secrete proteases, resulting in altered spectrin structure. Further membrane alteration and fragmentation occur due to differential pH and osmotic forces in tubular fluid, resulting in loss of hemoglobin and forming hypochromic dysmorphic RBC.22-26

RBC cast formation occurs due to trapping of RBCs within the tubular lumen by Tamm-Horsfall glycoprotein, aided by the acidic urine milieu (Fig 3).27,28 If blood enters cortical tubules secondary to tubulointerstitial injury, RBC casts can form without glomerular injury.7,29

Hematuria in Glomerular Diseases

Glomerular hematuria is an indication of altered glomerular structure; however, the severity of injury varies from overt glomerulonephritis to minor structural abnormalities. It may occur in the setting of isolated hematuria with minimal or no proteinuria. In such cases, the most common causes are IgAN, thin basement membrane (TBM) nephropathy, and mesangial proliferative GN, with 10%-20% of biopsies showing no detectable pathologic abnormality.30-32 Although microscopic hematuria and dysmorphic RBCs are cardinal signs of “nephritic syndromes,” they may occur in any form of glomerular disease.33,34 They may also be seen in nephrotic syndrome, although not a defining feature. In an international study of children with nephrotic syndrome, 22% of minimal change disease (MCD), 48% of focal segmental glomerulosclerosis (FSGS), and 58% of membranoproliferative GN had microscopic hematuria.35 Retrospective studies in adults have shown that microscopic hematuria is seen in up to 30% of patients with MCD,36 up to 40% with FSGS,37 and up to 50% with membranous nephropathy.38 Microscopic hematuria may be seen in diabetic kidney disease (DKD); it is found in up to 35% of patients, even with RBC casts present.39-41 Glomerular hematuria based on a high number of dysmorphic RBCs (≥80% of excreted RBCs) and acanthocyturia (≥5% of excreted RBCs) has been reported in 3% and 4% of patients with DKD, respectively.42,43 However, glomerular hematuria is rare in DKD and much less common than in

Figure 2. Passage of a red blood cell through the glomerular capillary to the urinary space. Electron microscopy showing an erythrocyte caught in action, diapedesing through the glomerular endothelium and basement membrane. Original image © 2001 Elsevier; reproduced from Collar et al19 with permission of the copyright holder.
patients with GN. The presence of glomerular hematuria should prompt a higher degree of suspicion for underlying nondiabetic glomerulopathy when present. In diabetic patients, in addition to absence of diabetic retinopathy and a duration of diabetes mellitus ≤5 years, glomerular hematuria (defined as >3 RBCs/HPF with >80% dysmorphosis) is a significant and independent risk factor for nondiabetic kidney disease. The most common disease states reported to be observed are membranous nephropathy and IgAN.39,44

IgA Nephropathy

IgAN is the most common primary glomerular disease worldwide and often presents with persistent hematuria. Macroscopic hematuria coincident with an upper respiratory tract or gastrointestinal infection is frequently present.5,45,46 IgAN is the most common cause of asymptomatic chronic hematuria and proteinuria, as demonstrated by mass school screening programs in South Korea.47,48 Although episodic gross hematuria in IgAN does not necessarily portend adverse kidney outcomes,59 persistence of microscopic hematuria may be a risk factor for progression to kidney failure, particularly when occurring with other markers of glomerular injury such as proteinuria. Sevillano et al50 demonstrated this after systematically repeating urine sediment testing in 112 patients with IgAN: hematuria (defined as >5 RBCs/HPF on microscopy) was time-averaged to identify individuals with persistent hematuria. Persistent hematuria was an independent risk factor for kidney failure, giving a 2.8-fold greater risk, similar to time-averaged proteinuria >0.75 g/d (2.8-fold greater risk) and to interstitial fibrosis and tubular atrophy on biopsy (3.1-fold greater risk). In the subgroup analysis, individuals with persistent hematuria and proteinuria >0.75 g/d had the worst prognosis. The combination of persistent glomerular hematuria and proteinuria in IgAN may be an important and easily identifiable predictor for adverse outcomes. Future studies should be performed to test this composite predictor for outcomes and response to treatment.

ANCA Vasculitis

Microscopic examination of the urine is an important component to the diagnosis and monitoring of kidney involvement in antineutrophil cytoplasmic antibody (ANCA)-vasculitis (AAV). Histopathological confirmation remains the gold standard for distinguishing AAV from other glomerular diseases, but urine sediment abnormalities found on microscopy have been used as a surrogate for biopsy-confirmed kidney involvement. In lieu of a kidney biopsy, the recent Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody-Associated Vasculitis (PEXIVAS) trial allowed inclusion of participants with glomerular hematuria and proteinuria in combination with positive ANCA serology.51 The Birmingham Vasculitis Activity Score (BVAS) deems the presence of hematuria (defined as 1+ blood on urinalysis or greater, or microscopy with >10 RBC per mL) as a marker of active disease.52-54 Although the BVAS is a validated, frequently used tool for assessment of disease activity in clinical trials, clinicians should be aware of its pitfalls and limitations. Non-glomerular causes of hematuria could be present.
including urinary tract infection, prostate disease, cyclophosphamide-induced cystitis, urinary tract malignancies, and other urinary tract diseases. Microscopic examination of urine sediment is essential not only for diagnosis but also for monitoring disease activity during treatment and follow-up. Although glomerular hematuria in a patient with positive ANCA is highly suggestive of AAV and pauci-immune GN, kidney biopsy remains the gold standard. We and others have seen many cases of glomerular hematuria in patients with positive ANCA who have alternative disease findings when biopsied. Geetha et al 55 reported 9 patients with small vessel vasculitis (8 AAV, 1 ANCA-negative) who underwent repeat kidney biopsy for persisting or new-onset hematuria but were otherwise in ongoing remission. None of the patients had active vasculitis; 2 had crescentic IgA, 2 had FSGS, 2 had evidence of arteriosclerosis only, and 3 had evidence of healed crescentic GN.

Hematuria has been evaluated as a tool to predict risk for adverse outcomes from AAV. Due to differing methodologies and varying definitions for hematuria, the studies cannot be compared head to head. Lv et al 56 examined 219 patients with AAV in clinical remission after induction therapy. Over a median 3-year follow-up period, the patients with persistent hematuria (>3 dysmorphic RBC/HPF) since diagnosis (80 of 219 [37%]) had a significantly greater decline in estimated glomerular filtration rate (eGFR) with 3.3-fold greater risk for doubling of serum creatinine or kidney failure when compared with the patients who experienced resolution of hematuria after induction therapy.

Not all studies consistently show hematuria as a risk factor for AAV relapse. Chen et al 57 found that among 55 patients with AAV, the persistence of hematuria (21 of 55 [38%]), defined as >5 RBC/HPF (on urine dipstick) 90 days after biopsy-confirmed diagnosis of AAV, was not associated with worse kidney function at 1 year compared with patient’s whose hematuria was resolved at 90 days (34 of 55 [62%]).

The variability in defining hematuria—including hematuria by positive dipstick urinalysis versus microscopic examination for dysmorphic RBCs and acanthocytes—hinders its use as a reliable risk predictor. Confirming the glomerular origin of hematuria through observation of dysmorphic RBCs and RBC casts as well as demonstrating increases in hematuria over time may provide better accuracy for hematuria to predict relapses. 56, 58 Repeating a kidney biopsy could be helpful to assess disease activity in certain cases of persistent or worsening hematuria when there is uncertainty of an active flare.

**Lupus Nephritis**

Systemic lupus erythematosus (SLE) frequently affects the kidneys, leading to GN classified as lupus nephritis (LN). The first diagnostic classification of SLE in 1971 included the presence of cellular casts (RBC, granular, hemoglobin, tubular, or mixed) on urine microscopy as one of the 14 diagnostic criteria. 59 This criterion was kept throughout subsequent revisions and carried over into the 2012 Systemic Lupus Erythematosus Collaborating Clinics (SLICC) classification criteria, in which the presence of RBC casts on urine microscopy is considered a marker for LN. 60 The gold standard method for diagnosing LN remains confirmation by kidney biopsy. A biopsy is also essential to determine the severity, activity, and chronicity of disease, which may guide treatment decisions.

Hematuria and urine sediment abnormalities remain frequently used tools to screen for and monitor LN disease activity. In a retrospective study of 323 SLE patients with isolated hematuria (urine sediment showing >5 RBC/HPF, no menses or infection, proteinuria <500 mg/d), 22 patients underwent a kidney biopsy: 96% (21 of 22) demonstrated LN, with 36% (8 of 22) showing proliferative LN (4 patients with class III, and 4 patients with class IV). 61 This highlights the fact that even without significant proteinuria, isolated hematuria may be a marker for proliferative LN. A prospective study evaluated the correlation between hematuria and severity of disease in 51 SLE patients with biopsy-confirmed nonproliferative LN (class I, II, or pure V; n = 18) or proliferative LN (class III or IV ± V; n = 33). Urine was collected before biopsy and analyzed for dysmorphism and quantity of RBCs using a well-defined, systematic approach. The amount of hematuria and acanthocyturia positively correlated with severity of National Institutes of Health LN Activity and Chronicity Index scores on biopsy (σ of 0.65 and 0.60, respectively, P < 0.0001 for both). There was good discriminatory ability for detecting proliferative LN (receiver operating characteristic of 0.83 and 0.81, respectively). 62

Long-term data from the Euro-Lupus trial was analyzed to evaluate for predictors of good kidney outcomes (defined as serum creatinine <1 mg/dL) at 7 years. Proteinuria <0.8 g/d was found to be the best predictor (sensitivity: 81%; specificity: 78%; positive predictive value: 88%; negative predictive value: 67%). Absence of hematuria (<5 RBC/HPF) did not perform as well (sensitivity: 62%; specificity: 64%; positive predictive value: 78%; negative predictive value: 45%). The addition of urine RBCs to proteinuria at 12 months as a composite predictor actually worsened the diagnostic accuracy, particularly for sensitivity (47%). 63 This once more highlights the importance of confirming the glomerular nature of hematuria when interpreting urine findings in LN, particularly among women of reproductive age in whom menstrual bleeding may lead to false-positive results. Most studies examining the clinical use of hematuria in SLE and LN do not account for dysmorphism or cellular casts. In 2007, the American College of Rheumatology (ACR) published criteria for defining LN response in clinical trials; they recognized that an active urine sediment (defined as >5 RBC/HPF and >5 white blood cells/HPF
and/or ≥1 cellular casts) may be used, while acknowledging its unreliability. Its use is recommended only if reproducibility can be demonstrated.65,66 Because of these pitfalls, urine sediment abnormalities have been removed from the most recent European League Against Rheumatism (EULAR)/ACR SLE classification as criteria for kidney involvement, replacing it with biopsy-confirmed LN even at the expense of a potential decrease in sensitivity.65,66 Although there seems to be a progressive move away from reliance on urine sediment abnormalities in LN, it remains a low-risk, low-cost endeavor that can provide valuable information to the clinician who incorporates the findings into the full clinical picture.

Hematuria in Other Forms of Glomerular Disease

As expected, glomerular hematuria is a presenting sign of many glomerular diseases, including inflammatory and noninflammatory glomerular disorders. TBM and Alport syndrome are common noninflammatory etiologies of glomerular hematuria. All male individuals with X-linked Alport syndrome and both males and females with autosomal recessive Alport syndrome have persistent microhematuria. About 90% of females heterozygous for X-linked Alport syndrome have microscopic hematuria. Glomerular hematuria may be intermittent or persistent in patients with TBM. Analogous to IgAN, both TBM and Alport syndrome may also present with gross synpharyngitic hematuria.68-71 Among other factors, gross hematuria in childhood has been associated with poor outcomes in X-linked Alport syndrome.72 Also, TBM may be coincidentally diagnosed with other GNs such as IgAN or even LN.73,74

Other rarer forms of GN such as C3GN or infection-related GN nearly always present with microscopic hematuria and possibly with RBC casts and a nephritic picture.75-77 These disease entities are quite rare, such that the current literature has not examined the significance of glomerular hematuria as a predictor of long-term kidney outcomes defined by severity of kidney dysfunction and proteinuria. Anti-GBM disease is probably the most inflammatory and severe of all GNs, so it is expected to be characterized by marked urinary sediment abnormalities abounding with acanthocytes and RBC casts.78 Anticoagulation-related nephropathy, a newly recognized cause of acute kidney injury, frequently presents with glomerular hematuria and has been associated with warfarin and other oral anticoagulants. The exact mechanism is unclear because glomeruli typically have no specific lesions or alterations, but dysmorphic RBCs are seen on microscopy, and tubules show evidence of RBC casts.79

How Should Urine Sediment Analysis Be Used?

Nearly every nephrology trainee learns microscopic examination of urine to evaluate glomerular disease. It is a conceptually pleasing and rewarding process using visual inspection to help diagnose a disease in a rapid and noninvasive manner.

Urine microscopic analysis always begins with sample collection, transportation, and preparation. This pre-analytical phase can be the source of problems. Improper storage, the duration and force of centrifugation, or the method of pellet resuspension can all affect the accuracy of the results during urine microscopy.80-82 Classically, microscopy is carried out when a dipstick test urinalysis flags abnormal results. Many automated microscopic urine analyzers now remove the manual preparation steps and integrate test strip readings with automated cell counts. These devices are less labor intensive than manual microscopy, allow processing many urine samples at once, correlate well with number of cells/HPF with manual cell counts, and can identify cellular casts.83,84 However, automated microscopic urinalysis devices may not properly identify dysmorphic cells and may be unable to specify type of cellular cast, resulting in limited accuracy in pathological urine samples.82,84,85 This limits their use when evaluating for a glomerular origin to hematuria. Urine specimens flagged as abnormal must still be manually inspected by trained staff to identify important abnormalities such as dysmorphic RBCs or RBC casts. In our experience, urine with a completely negative dipstick may contain RBC casts; thus, one can argue there is always a benefit to be had from microscopic examination of urine in the appropriate clinical context.

Because urine microscopy remains an operator-dependent process, concerns over reproducibility exist even among nephrologists. In an assessment of interobserver reliability, about 90% of nephrologists agreed on dysmorphic RBCs while only 60% agreed on RBC casts, likely due to their rarer presence overall.86 Despite these limitations, evidence of glomerular hematuria on urine microscopy (dysmorphic RBCs, acanthocytes, RBC casts) has been consistently shown in studies to have high specificity for glomerular disease and GN. Although there is no standard, widely accepted definition of what constitutes glomerular hematuria, presence of ≥40% dysmorphic RBCs or ≥5% acanthocytes in 2 of 3 urine samples may be considered as glomerular in origin.87

Despite the inherent limitations, observing urine sediment abnormalities clearly has utility. Much like serum creatinine or proteinuria measurements, it cannot be the sole basis for diagnosis or decision making. However, given their high specificity for GN, urine sediment abnormalities suggestive of glomerular disease may be valuable for management decisions when there is a high pretest probability for GN. Standardizing both the methodology of urine sediment analysis and the definition of glomerular hematuria would be a valuable benchmark for future clinical investigations. Finally, urine microscopy is an important teaching tool for students and trainees, which aids in understanding glomerular pathology and highlights the fundamental importance of bedside medicine.
Article Information

Authors' Full Names and Academic Degrees: Manish K. Saha, MD, David Massicotte-Aznarouch, MD, MSc, Monica L. Reynolds, MD, MSCR, Amy K. Mottl, MD, MPH, Ronald J. Falk, MD, J. Charles Jennette, MD, and Vimal K. Derebail, MD, MPH.

Authors' Affiliations: UNC Kidney Center, Division of Nephrology and Hypertension, Department of Medicine (MKS, DM-A, MLR, AKM, RJF, VKD), and Department of Pathology and Laboratory Medicine, School of Medicine (JCJ), University of North Carolina, Chapel Hill, North Carolina.

Address for Correspondence: Manish K. Saha, MD, Division of Nephrology and Hypertension, University of North Carolina at Chapel Hill, UNC Kidney Center, 7024 Burnett-Womack/CB # 7155, Chapel Hill, NC 27599-7155. Email: manish_saha@med.unc.edu

Support: None.

Financial Disclosure: Dr Saha has received honoraria from Traveure, ChemoCentryx, and Elsevier. Dr Mottl has received royalties from UpToDate, consultancy fees from Bayer, and research support from Alexion, Protalix Bio Therapeutics, Sangamo Therapeutics, jubilant Therapeutics, and NIH/NIDDK. Dr Derebail serves on an advisory board for Travere, Merck, and Bayer, and has received consultancy fees from Novartis and royalties from UpToDate. The other authors declare that they have no relevant financial interests.

Acknowledgements: The authors would like to thank Pablo Ariel, PhD, Director of Microscopy Services Laboratory at UNC, Chapel Hill, UNC Kidney Center, Division of Nephrology and Hypertension, Department of Medicine (MKS, DM-A, MLR, AKM, RJF, VKD), and Department of Pathology and Laboratory Medicine, School of Medicine (JCJ), University of North Carolina, Chapel Hill, North Carolina. Dr Derebail serves on an advisory board for Travere, Merck, and Bayer, and has received consultancy fees from Novartis and royalties from UpToDate. The other authors declare that they have no relevant financial interests.

Peer Review: Received September 22, 2021. Evaluated by 2 external peer reviewers, with direct editorial input from an Associate Editor and a Deputy Editor. Accepted in revised form February 16, 2022.

References


