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DYSMORPHIC RED BLOOD CELLS IN URINE – EVALUATION AND SIGNIFICANCE

Nephrology

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ABSTRACT

Hematuria is a common pathological finding in urine examination. A detailed clinical history and examination along with relevant testing is required to find the cause of hematuria. It can be a sign of glomerulonephritis and if not diagnosed on time can lead to chronic renal failure. Documenting dysmorphic RBC in urine helps in diagnosing glomerular hematuria. Phase contrast microscopy is considered gold standard in identifying dysmorphic RBCs but new evidence shows that light microscopy is equally effective. Routine reporting of dysmorphic RBCs should be done in all patients of hematuria. Various methods to increase identification of dysmorphic RBCs are discussed.

KEYWORDS

Dysmorphic RBC, Glomerulonephritis, Hematuria

INTRODUCTION

The prevalence of asymptomatic microscopic hematuria in adults ranges from 0.19% to 21 % [1]. The importance lies in the fact that it is an important sign of intrinsic renal disease. In routine practice a prevalence of 5% is seen but depends on the definition of hematuria, age, sex and population studied [2]. As low as 1 ml of blood per one litre of urine can lead to grossly visible hematuria. Red colour of urine can also be due to hemoglobin or myoglobin which can be distinguished by microscopy of urine. Hematuria can be a sign of glomerular diseases and can progress to end stage kidney disease if not identified early. On the other hand it can also be a sign of urological malignancy in upto 10% cases [3]. So a correct approach would be to understand the underlying cause of hematuria by obtaining a detailed clinical history and physical examination of the patient which will help to exclude many causes.

First, infections of the urinary tract should be ruled out on the basis of history of dysuria, frequency, flank pain, leukocyte esterase, nitrites, WBC and bacteria in urine. If infection is present, patient should be treated and reevaluated after 4 weeks for presence of hematuria. Vigorous exercise, urethral trauma, urological intervention and menstruation should be ruled out. Ultrasound, CT scan imaging and urine cytology help in identifying various urological causes. Hypertension, proteinuria, raised serum creatinine, dysmorphic RBCs and RBC casts point towards glomerular diseases.

HEMATURIA DETECTION METHODS

Dipstick test of urine is simple, less time consuming and does not require highly trained staff but may be misleading as it lacks the ability to distinguish RBC from myoglobin or hemoglobin. Dipsticks can be very sensitive even in physiological levels of RBC in urine. A false negative dipstick test can be ca used by high doses of vitamin C.

Microscopic examination of the urine overcomes the shortcoming of dipstick test. The definition of microscopic hematuria varies in various studies from 1 to 10 RBC/HPF but routinely ≥ 3 RBC/HPF is taken as abnormal. The importance of identifying glomerular hematuria cannot be underestimated. Therefore we evaluated the methods available for its identification. Birch and Fairley (4) reported less than 2000 RBC/ml as normal. Various reports have considered less than 8000 RBC/ml as normal[4,5,6]. Greater than 80% dysmorphic RBC is regarded as a sign of glomerular hematuria. Greater than 80% normomorphic RBC suggests non glomerular hematuria. Microscopic hematuria in patients with biopsy proven isolated diabetic nephropathy has been reported in 32.3% to 78% [7]. Dysmorphic erythrocytes proved superior to hematuria for indicating non diabetic renal disease in type 2 diabetic patients [8].

Though the importance of dysmorphic RBCs is well documented, their routine testing in patients with hematuria is not widely practiced. This is mainly due to lack of trained technical personal as well as lack of standardized definition of dysmorphic RBC.

The dysmorphic changes in Red Blood cell morphology occur due to mechanical damage when passing through glomerular basement membrane and from osmotic damage while passing through the nephron (Figure 1). RBC dysmorphic characteristics were proposed by Birch and Fairley [4]. He considered 3 different types of cell population in dysmorphic RBC.

Hans Kolher et al [9], in 1991 observed that > 5% acanthocytes and codocytes were frequently related to glomerulopathy. Tomita et al [10] classified RBC in five glomerular types (G1-G5) and five non glomerular types (N1-N5). Among these > 15% glomerular form or > 5% G1 form was associated with glomerular hematuria. Acanthocytes show a vesicle like protrusion and their assessment is more reproducible than count of dysmorphic cells. A count of more than 5% is highly specific (98%) of glomerular disease.

Light microscopy, phase contrast microscopy or automated cell counters can be used to document dysmorphic RBC. Automated cell counters can determine the MCV of RBC. A Value of less than 74 fL- predicts glomerular hematuria (sensitivity 76% and specificity 74%) [11]. Concentration based techniques, used in patients with RBC dysmorphism, increase the detection rate of RBC casts as compared to standard method [12]. The presence of RBC casts in the urine of patients with dysmorphic hematuria is a marker of glomerular hematuria. Even a single RBC cast indicates glomerular hematuria [13]. Increased detection of the patients of glomerular hematuria is important as this is a progressive condition and leads to CKD. Phase contrast microscopy and automated urine analysis are not easily available in most clinical laboratory. One study has reported evaluation of dysmorphic RBC by light microscopy with lowering of the condenser lens; and found it to be equal or more effective than phase contrast microscopy [14].

Dysmorphic RBC threshold of ≥ 25% in one study has shown a sensitivity of 20.4%, specificity of 96.3% and positive predictive value of 94.6% for glomerular diseases [15]. Urinary RBC >10/HPF were highly predictive of glomerulonephritis.

Study by Yu Chu-Su et al [16] has reported a total of 28 types of isomorphic and dysmorphic RBC's using bright field microscopy with results comparable to phase contrast microscopy. They have suggested that the main problem with assessment of urine microscopy sediment may be related to the laboratory preparation of the sample depending

on sample volume, relative centrifugal force (RCF), centrifuge duration, concentration factor and method of observation. The author has suggested a use of 500g force t o centrifuge the urine rather than 400g.

Most lab technicians follow Clinical and Laboratory standard institute (CLSI) protocols [17] . According to this, 12 ml of urine is centrifuged at an RCF of 400g for 5 minutes, pallet resuspended in 1 ml with 12 fold concentration method. Most guidelines suggest 10 ml urine should be used. Some people use RPM instead of RCF. RCF (g) = 1.118 x 10^{-5} x radius (cm) x RPM. All guidelines recommend centrifugation for 5 minutes. An increase in sediment concentration to 20 fold can be achieved by resuspending the sediment pallet in 0.5 ml of supernatant. This can contribute to increase in detection of formed elements. Some guidelines have recommended use of staining techniques with sternheimer stain to increase the contrast between the different formed elements of the urine [18,19].

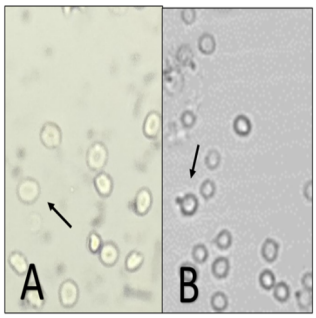
Some centers apply drop of resuspended urine sediment on a slide with coverslip. Since the volume of urine examined in this fashion may vary, use of counting chamber can increase the reproducibility of results.

Isomorphic RBC are biconcave, their central pallor is about half of the diameter of an RBC. They can swell to spheres or shrink to spiked discs in urine. The margins of central pale area is smooth in isomorphic RBC. In dysmorphic RBC the central pale has uneven margins or has a target spot. Some dysmorphic RBC even have blebs/ projections [16].

CONCLUSION

We want to highlight that isolated hematuria is a common problem in the community. Correct stepwise approach to rule out infection and other common causes by taking detailed history taking and examination is important. Detailed urine examination with special emphasis to evaluate for dysmorphic RBCs help in early identification of glomerular diseases. This can prevent progression of kidney disease and save many lives. Efforts should be made for standardization of urine sediment preparation and training of medical laboratory technologists in identification of dysmorphic RBCs. Reporting of dysmorphic RBC should be routine in all patients of hematuria. Dependence on phase contrast microscopy, a less available method, should be reduced and normal bright field microscopy should be used to detect dysmorphic RBCs. Urinary sediment staining techniques should also be developed. These efforts will help in early diagnosis of glomerulonephritis and reduce its progression to chronic renal failure.

Figure 1



Red Blood cell morphology (light microscope x400).

A - isomorphic RBCs. B - dysmorphic RBCs

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