

URINARY ERYTHROCYTE MORPHOLOGY AS A DIAGNOSTIC AID IN HAEMATURIA

G Ahmad, M Segasothy, Z Morad

ABSTRACT

The value of urinary erythrocyte morphology in diagnosing glomerular and non glomerular haematuria was studied using phase contrast microscopy in 105 patients with significant haematuria. Fifty-eight (93.6%) out of 62 patients with glomerulonephritis had dysmorphic erythrocytes and 40 (93.1%) out of the 43 patients with nonglomerular disease had isomorphic erythrocytes in the urine. A mixed picture of glomerular and nonglomerular haematuria was seen in 5 patients. The sensitivity was 93.6%, the specificity was 97.7% and the positive predictive value was 98.3% for glomerulonephritis in patients with dysmorphic haematuria. The positive predictive value for a nonglomerular source of bleeding was 96.7% with isomorphic haematuria. It is concluded that phase contrast microscopic examination of erythrocytes in urine is a simple, inexpensive and noninvasive technique that reliably distinguishes between glomerular and nonglomerular bleeding in patients.

Keywords: haematuria, glomerular bleeding, nonglomerular bleeding, phase contrast microscopy.

SINGAPORE MED J 1993; Vol 34: 486-488

INTRODUCTION

Haematuria is a common diagnostic problem in clinical practice and may result from renal, urologic or systemic diseases. Haematuria due to glomerulonephritis may not always be associated with the presence of red cell casts⁽¹⁾ or proteinuria⁽²⁾ and may hence be difficult to distinguish from haematuria from the lower urinary tract. A simple, reliable and non-invasive method of differentiating glomerular from nonglomerular source of haematuria will enable one to plan appropriate investigations without subjecting the patients to unnecessary invasive procedures.

Birch and Fairley⁽³⁻⁶⁾ have reported that urinary erythrocytes of glomerular origin are dysmorphic using phase contrast microscopy. Conversely erythrocytes of nonglomerular origin are isomorphic. Their findings have subsequently been confirmed by numerous studies⁽⁷⁻¹¹⁾. In a developing country where resources and the patients' acceptance for invasive procedures are limited, the ability to diagnose the cause of haematuria by this method would be of great value. We therefore tried to assess the value of microscopic analysis of erythrocyte morphology using phase contrast microscopy in identifying the source of bleeding in patients with haematuria in the local context.

PATIENTS AND METHODS

One hundred and twenty consecutive patients with haematuria were identified from the nephrology and urology inpatient and outpatient populations. A single-blind coding protocol was fol-

lowed during analyses to ensure that the investigators were unaware of the clinical diagnosis. Midstream urine samples from the patients were examined within one hour of collection. Erythrocyte numbers were assessed in uncentrifuged urine whilst erythrocyte morphology was assessed in centrifuged urine. Erythrocyte morphology was assessed only when significant haematuria (>13000 cells/ml) as defined by Fairley⁽⁶⁾ was present. 10ml of urine was centrifuged at 2000 rpm for 5 minutes in a centrifuge with a swing-out head. 9.5 ml of supernatant was removed and the sediment was resuspended in 0.5 ml of supernatant. One drop of sediment was examined in a Fuchs-Rosenthal chamber using phase contrast microscopy (Olympus BH microscope equipped with phase contrast illumination, x 400).

Erythrocyte morphology was assessed as either glomerular (dysmorphic) (Fig 1) or nonglomerular (isomorphic) (Fig 2) as reported previously by Birch and Fairley⁽³⁻⁶⁾. Haematuria was considered 'glomerular' if erythrocytes in the urine showed a wide range of morphologic variation, frequently with loss of haemoglobin. 'Nonglomerular' haematuria was diagnosed where erythrocytes were morphologically uniform with not more than two cell populations present. Urine samples containing an even proportion of glomerular and nonglomerular erythrocytes were called mixed. The sediment was also examined for the presence of red cell casts and uncentrifuged urine samples were analysed with dipstick (Combi 9) for albumin, pH and blood.

The diagnosis was established by an independent observer who was unaware of the urine findings using results of investigations in radiology, cystoscopy and renal biopsy.

RESULTS

In 15 out of the 120 patients, the urinary erythrocyte count was less than 13000/ml. The urine samples from these patients were not studied further. The remaining 105 patients (87.5%) had significant haematuria as defined earlier. Sixty-two of these patients had glomerulonephritis of various types proven by renal biopsy (Table I). The mean urinary erythrocyte count in these patients was $90,000 \pm 61,000$ (range: 14,000 – 200,000) cells/ml. Forty-three patients had nonglomerular disease proven by radiology and/or cystoscopy (Table I). The mean urinary erythrocyte count in these patients was $123,000 \pm 80,000$ (range: 15,000 – 270,000 cells/ml). Fifty-eight (93.6%) out of the 62 patients with glomerulonephritis had dysmorphic erythrocytes in the urine and 40 (93.1%) out of the 43 patients with nonglomerular disease had isomorphic cells in the urine (Table II). This difference is highly significant ($p < 0.001$), using chi-square test.

A mixed picture of glomerular and nonglomerular haematuria was seen in 5 patients (renal calculi - 1, polycystic kidney disease

Department of Nephrology
General Hospital
Kuala Lumpur
Malaysia

G Ahmad, MBChB Hons (Dublin), MRCPI, M Med (UKM)
Clinical Specialist

Z Morad, FRCP (Edin)
Consultant Nephrologist and Head

Department of Medicine
Faculty of Medicine
Universiti Kebangsaan Malaysia
Jalan Raja Muda Abdul Aziz
50300 Kuala Lumpur
Malaysia

M Segasothy, MD (Mel), FRCP (Glas), FRCP (Edin), FRCP (Lond)
Associate Professor

Correspondence to: Dr M Segasothy

– 1, IgA nephropathy – 1, diffuse proliferative glomerulonephritis – 1, membranoproliferative glomerulonephritis – 1).

Table 1 – Clinical diagnosis in 105 patients with haematuria

Diagnostic group	Number of patients
<i>Glomerular disease</i>	
IgA nephropathy	18
Membranous GN	17
Diffuse proliferative GN	12
Focal segmental proliferative GN	5
Crescentic GN	3
Focal glomerulosclerosis	3
Membranoproliferative GN	2
Focal necrotising GN	2
<i>Nonglomerular disease</i>	
Renal calculi	36
Carcinoma of bladder	6
Polycystic kidney disease	1

GN : glomerulonephritis

Table II – Pattern of erythrocyte morphology in urine samples from 105 patients with haematuria

Diagnostic group	Number of patients showing		
	Dysmorphic cells	Isomorphic cells	Mixed morphology pattern
Glomerulonephritis	58 (93.6%)	1 (1.6%)	3 (4.8%)
Nonglomerular disease	1 (2.3%)	40 (93.1%)	2 (4.6%)
Total	59	51	5

DISCUSSION

This study has confirmed that determination of erythrocyte morphology using phase contrast microscopy is a highly accurate method to differentiate glomerular from nonglomerular haematuria. For glomerular bleeding the sensitivity was 93.6% the specificity was 97.7% and the positive predictive value was 98.3%. For nonglomerular bleeding the positive predictive value was 96.7%. Thus on the basis of erythrocyte morphology it would be possible to channel patients with haematuria towards appropriate investigations. Patients presenting with glomerular haematuria associated with or without red cells casts and proteinuria would need a renal biopsy, and patients presenting with nonglomerular haematuria would need urologic and/or radiologic evaluation.

A mixed picture of glomerular and nonglomerular haematuria was seen in 5 patients and was associated with IgA nephropathy, diffuse proliferative and membranoproliferative glomerulonephritis, renal calculi and polycystic kidney disease. Birch and Fairley^(4,5) have reported mixed haematuria in IgA nephropathy whilst Fasset and co-workers⁽⁷⁾ have reported its occurrence in patients with renal calculi, IgA nephropathy, mesangiproliferative glomerulonephritis, membranous glomerulonephritis, mesangiocapillary glomerulonephritis, systemic lupus erythematosus and diabetic nephropathy. The cause for mixed haematuria is unclear. Fairley and Birch suggest that vascular lesions might be present in the mucosa of the urinary tract in patients with IgA nephropathy which could account for some nonglomerular bleeding in this type of glomerulonephritis⁽⁴⁾.

Doubts have been expressed regarding the diagnostic reliability of phase contrast microscopy⁽¹²⁾. Inter-observer variation, lower specificity and sensitivity⁽¹²⁾ have also been reported. The criteria for diagnosing glomerular bleeding have varied. Some have diagnosed glomerular bleeding when more than 80% of the cells are dysmorphic and nonglomerular bleeding when more than 80% of the cells are isomorphic⁽⁷⁾. Others have regarded more than 75% dysmorphism as indicative of glomerular bleeding and more than 83% isomorphism as indicative of nonglomerular bleeding⁽¹⁰⁾.

In order to overcome observer variability, the Coulter counter which estimates erythrocyte size has been used to distinguish glomerular from nonglomerular bleeding⁽¹³⁻¹⁶⁾. None of these studies compared this technique with phase contrast microscopy. Two recent studies comparing these techniques have found both to be reliable and sensitive^(17,18).

The cause for the dysmorphic shape of erythrocyte is not known. It has been postulated that erythrocytes acquire this shape as a result of mechanical stress when the cells pass through defects in the glomerular basement membrane⁽¹⁹⁾ and as a result

Fig 1 – Glomerular (dysmorphic) erythrocytes (x 400)

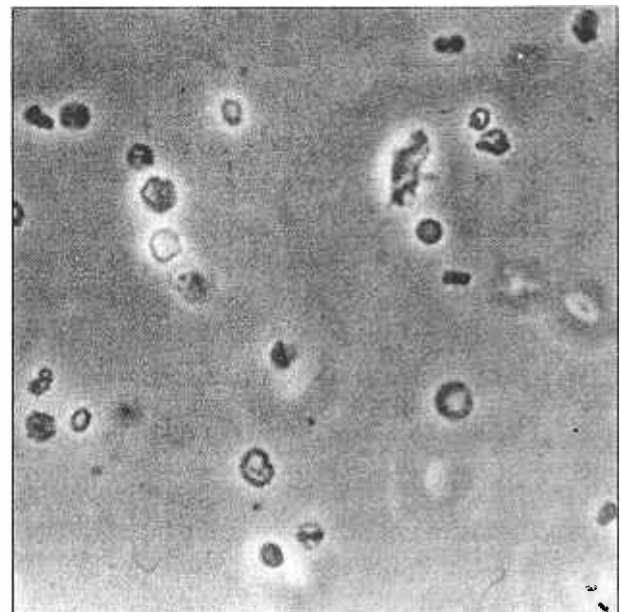
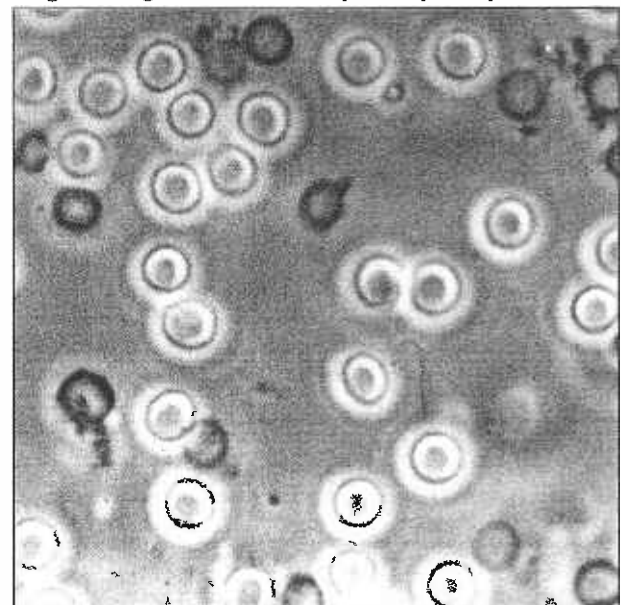


Fig 2 – Nonglomerular (isomorphic) erythrocytes (x 400)



of changes in osmolality and pH as the erythrocytes pass through the renal tubules⁽⁵⁾. Recently, it has been shown that changes in pH and osmolality of the urine play a role in the causation of the dysmorphic shape⁽²⁰⁾.

In conclusion, our study confirms that phase contrast microscopic examination of erythrocytes in the urine is a simple, inexpensive and noninvasive technique that reliably distinguishes glomerular from nonglomerular haematuria. It enables the clinicians to select the most appropriate investigations, thereby avoiding unnecessary and invasive diagnostic procedures.

REFERENCES

1. Fairley KF. Presenting features of renal disease 2 - haematuria and proteinuria. *Med Intern* 1982; 1:1066.
2. Kincaid Smith P, Dowling JP. Glomerulonephritis. *Med J Aust* 1980; 25:1795-804.
3. Birch DF, Fairley KF. Haematuria: Glomerular or nonglomerular? *Lancet* 1979; ii:845-6.
4. Fairley KF, Birch DF. Haematuria: A simple method for identifying glomerular bleeding. *Kidney Int* 1982; 21:105-8.
5. Birch DF, Fairley KF, Whitworth JA, Forbes IK, Fairley JK, Cheshire GR, et al. Urinary erythrocyte morphology in the diagnosis of glomerular haematuria. *Clin Nephrol* 1983; 20:78-84.
6. Fairley KF. The value of urine microscopy in clinical nephrology. In: Suleiman AB, Morad Z, eds. *Proceedings of the Sixth Asian Colloquium in Nephrology, The seminar on renal transplantation, The postgraduate course in Nephrology, Hong Kong: Excerpta Medica Asia Ltd, 1985:27-31.*
7. Fassett RG, Horgan BA, Mathew TH. Detection of glomerular bleeding by phase contrast microscopy. *Lancet* 1982; i:1432-4.
8. Rizzoni G, Braggion F, Zacchello G. Evaluation of glomerular and nonglomerular haematuria by phase contrast microscopy. *J Pediatr* 1983; 103:370-4.
9. Chang BS. Red cell morphology as a diagnostic aid in haematuria. *JAMA* 1984; 252:1747-9.
10. Pollock C, Pei Ling L, Gyory AZ, Grigg R, Gallery EDM, Caterson R, et al. Dysmorphism of urinary red blood cells - value in diagnosis. *Kidney Int* 1989; 36:1045-9.
11. Schramek P, Schuster FX, Georgopoulos M, Porpacz P, Maier M. Value of urinary erythrocyte morphology in assessment of symptomless microhaematuria. *Lancet* 1989; ii:1316-9.
12. Raman GV, Pead L, Lee HA, Maskell R. A blind controlled trial of phase contrast microscopy by two observers for evaluating the source of haematuria. *Nephron* 1986; 44:304-8.
13. Shichiri M, Nishio Y, Oowada A, Tomita K, Shiigai T. Use of autoanalyser to examine urinary-red-cell morphology in the diagnosis of glomerular haematuria. *Lancet* 1986; ii:781-2.
14. Shichiri M, Nishio Y, Suenaga M, Tomura S, Hosoda K, Ogura M, et al. Red-cell volume distribution curves in diagnosis of glomerular and nonglomerular haematuria. *Lancet* 1988; i:908-11.
15. Dozzi D, Delvecchio C, Turci A, Turci F, Baldrali L, Martinelli A. Detection of glomerular bleeding by urinary-red-cell size distribution. *Nephron* 1988; 50:380-2.
16. Goldwasser P, Antignani A, Mittman N, Rao Y, Mushnick RA, Norbergs A, et al. Urinary red cell size: diagnostic value and determinants. *Am J Nephrol* 1990; 10:148-56.
17. Fairley K, Bennett WM, Fairley S, Birch D. Comparison of red cell volume distribution by Coulter counter (CC) to phase contrast microscopy (PCM) in the differentiation of glomerular (G) from nonglomerular (NG) haematuria. *Kidney Int* 1989; 36:1172.
18. de Caestecker MP, Hall CL, Basterfield PT, Smith JG. Localisation of haematuria by red cell analysers and phase contrast microscopy. *Nephron* 1989; 52:170-3.
19. Lin J, Wada H, Maeda H, Hattori M, Tanaka H, Uenoyama F, et al. Mechanism of haematuria in glomerular disease, an electron microscopic study in a case of diffuse membranous glomerulonephritis. *Nephron* 1983; 35:65-72.
20. Briner VA, Reinhart WH. In vitro production of glomerular red cells: role of pH and osmolality. *Nephron* 1990; 56:13-8.

Larry Chin paid \$680,000/- for a semi-detached house in Namely place two and a half years ago.

Today, the same property can fetch \$1.4 million

Is he happy to make \$720,000 for an investment of \$680,000/- within two and a half years? or does he think that his property will reach \$2 million?

Is it true that the best way to invest in property is to cash in on other's uncertainty and why?

Which is the best way to invest in property with minimum investment and maximum return?

Do you believe in investing in an area that not many people notice?

We, at **BOBIMARG COMPANY**, a licenced Real- Estate company established since 1975 have successfully put together numerous good deals during the 18 years have seen the greedy ones suffer and the wise one enjoy their fortune.

Please feel free to call us for the answers.

We are at your service on all matters relating to buying, selling, leasing of properties.

Call Mr. Ronald Ho/Phillip at Tel: 3392322 (5Lines)

Fax: 3391189/3363305

Ronald - 3183607 (Pager)

Phillip - 2137773 (Pager) 8261268 (H. Phone)

