Kidney International, Vol. 21 (1982), pp. 105–108

TECHNICAL NOTE

# Hematuria: A simple method for identifying glomerular bleeding

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Hematuria is a common diagnostic problem in clinical practice. The appearance of frank blood in the urine is a startling symptom that usually prompts the patient to consult his doctor and to be referred for investigation. Microscopic hematuria, although not evident to the patient, is being detected more frequently following the introduction of chemical screening tests, and this has greatly increased the number of patients being referred for investigation.

Current practice for the investigation of hematuria is set out in *Campbell's Urology* [1] as follows: "Hematuria may be gross or microscopic, but it must be emphasized that the degree of hematuria bears no relationship to the possible cause. Any red blood cells seen in a centrifuged specimen of urine must be considered significant. Hematuria should never be ignored, and no matter how trivial the bleeding may seem, a complete urological investigation into its cause is mandatory."

It has been widely assumed that proteinuria accompanies hematuria in patients with glomerular disease. Thus, the group of patients with hematuria and normal urinary protein may be subjected to extensive urologic investigations including cystoscopy, retrograde pyelography, and aortography. But some patients with glomerular bleeding do not have proteinuria, and if investigations are necessary in such patients, a more appropriate line of investigation would be renal function testing and renal biopsy. Our observations from a substantial number of urine samples examined over several years have suggested that glomerular bleeding can be distinguished from other causes of hematuria by careful microscopy of the urine sediment [2]. The present report sets out the results of a small study in which urine samples of patients with glomerulonephritis and others with bleeding from other sites in the urinary tract were examined using phase-contrast microscopy.

## Methods

Midstream urine samples were examined from 88 patients referred for investigation of hematuria. Renal biopsy was performed on all patients in whom the clinical presentation and urine findings (for example, proteinuria, presence of blood casts) suggested glomerular disease. The remainder were investigated by cystoscopy and appropriate radiologic methods.

A 10-ml fresh urine sample was centrifuged for 5 min at ×750g in a centrifuge with a swing-out head. From this, 9.5 ml of supernatant was removed, and the resuspended deposit was examined in a Fuchs-Rosenthal chamber, using phase-contrast microscopy (Olympus BH microscope equipped with positive phase-contrast illumination).

## Results

Glomerular disease was diagnosed in 58 of the 88 patients studied, and a nonglomerular lesion was identified in the remaining 30 patients (Table 1). In each case, the diagnosis was made on indisputable demonstration of the abnormality set out in Table 1. Hence, all patients with glomerular disease had renal-biopsy proof of the diagnosis, and even in those with minor glomerular changes, the presence of red blood cells in Bowman's space and renal tubules confirmed the glomerular source of bleeding. But, in 6 patients with minor glomerular changes, there was doubt that this was the full explanation of the hematuria. Thus, panendoscopy, pyelography, and arteriography were undertaken. These investigations, however, failed to show a urologic cause of the bleeding.

Dysmorphic red blood cells were seen in the urine sediment of 55 of 58 patients with glomerular disease and in none of 30 patients with nonglomerular disease ($P < 0.001$). In 3 patients with proven glomerulonephritis, urine microscopy showed a mixed population of cells. Although the majority of cells were dysmorphic, up to 20% of cells resembled those seen in nonglomerular bleeding.

Figure 1 illustrates the diversity of red cell morphology characterizing the urinary sediment in patients with glomerulonephritis. A representative selection of dysmorphic ("glomerular") cells is depicted in Figure 2 (a–l). Figure 2a and b, show cells appearing to have extruded small phase-dense blebs of cytoplasm from the cell membrane. Figure 2c shows a cell in which the limiting membrane appears to have ruptured with consequent loss of cytoplasm. The cell to the left in Figure 2d exhibits a similar appearance, although the residual cell body is markedly more phase-dense. The cell to the right in Figure 2e shows granular deposition of phase-dense material at intervals around the inner aspect of the cell membrane. Figure 2f contains a cell in which similar membrane deposits appear to have coalesced. Faint cytoplasmic extrusion can also be seen projecting from the cell membrane. Figure 2g shows a "cell" that is apparently devoid of its limiting membrane. A similar structure is present in Figure 2h, in which a number of phase-dense aggregates are evident in the cytoplasm. Figure 2i shows

Received for publication January 8, 1981
and in revised form April 30, 1981

0085-2538/82/0021-0105 $01.00

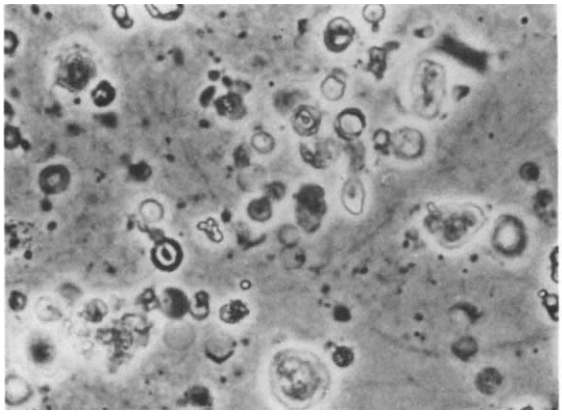

**Fig. 1.** *Urine sediment, glomerular bleeding.* (×1600).

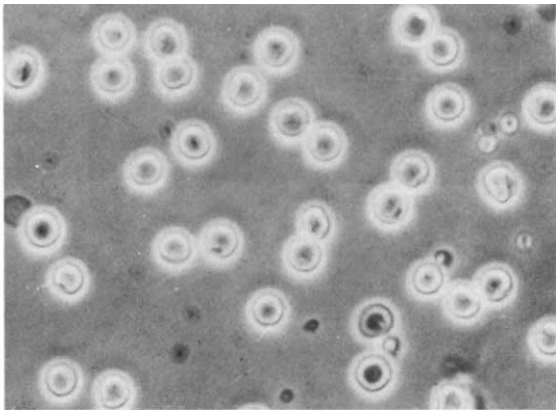

**Fig. 3.** *Urine sediment, nonglomerular bleeding.* (×1600).

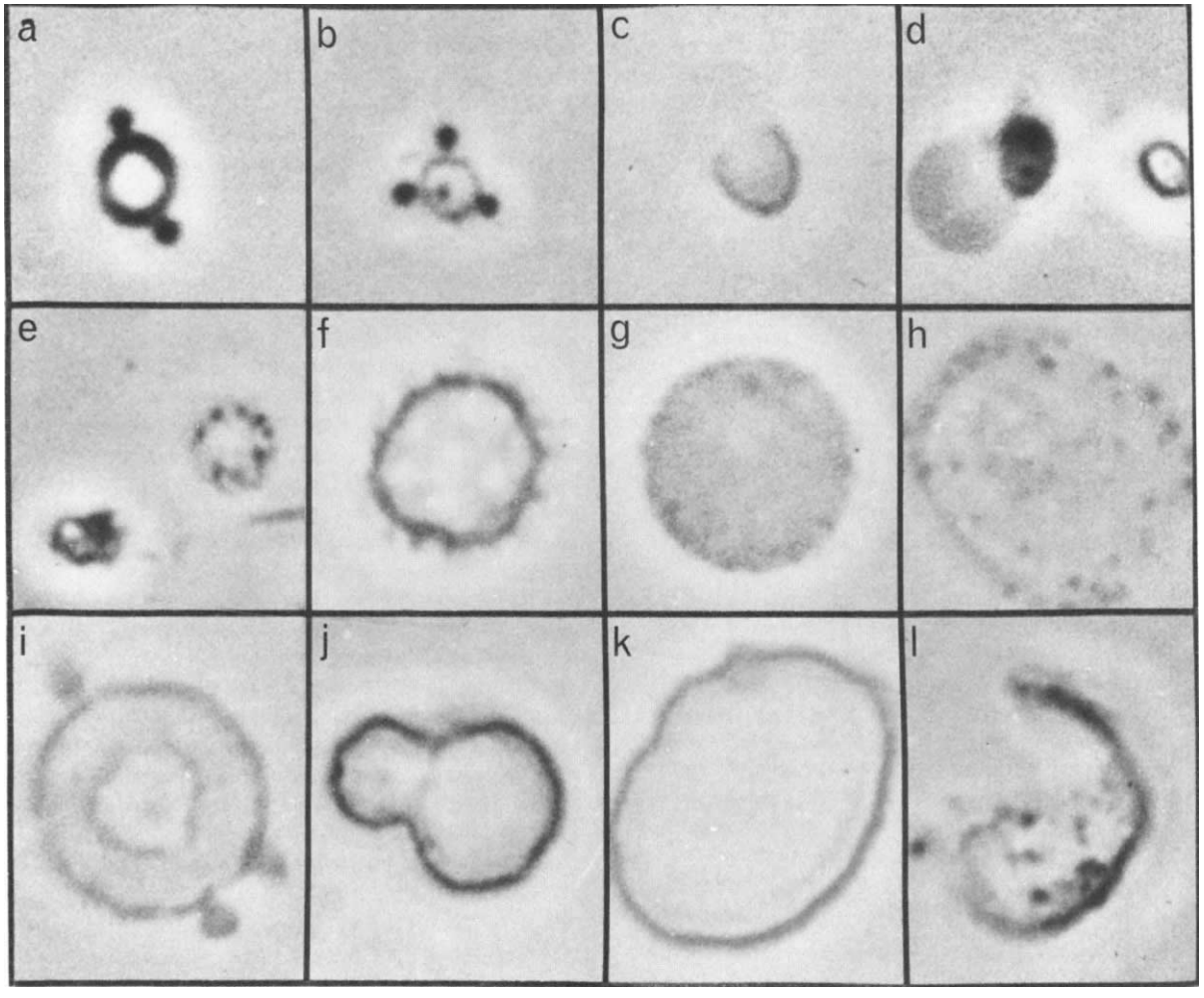


**Fig. 2.** *"Glomerular" red cells.* a–e ×4000, f–l ×10,000 (See text for detailed comments).

**Table 1.** Clinical diagnoses in 88 patients with hematuria

| Diagnostic group | No. of patients |
|---|---|
| Glomerular disease, biopsy proven with red blood cells in tubules | *58* |
| Minor glomerular changes | 11 |
| Membranous glomerulonephritis | 11 |
| Focal and segmental hyalinosis/sclerosis | 5 |
| Mesangial proliferative glomerulonephritis | 20 |
| Focal and segmental proliferative glomerulonephritis | 8 |
| Mesangiocapillary glomerulonephritis | 3 |
| Nonglomerular disease | *30* |
| Renal calculi (proven by radiography) | 9 |
| Inflammatory bladder polyps (proven by cystoscopy and histologic examination) | 3 |
| Acute renal papillary necrosis (classical lesions on radiography) | 3 |
| Polycystic kidney disease (classical lesions on radiography) | 6 |
| Carcinoma of bladder (proven by cystoscopy and histologic examination of tissue) | 4 |
| Acute cystitis (dysuria, frequency, pyuria, bacteriuria, and rapid response to antibiotics) | 3 |
| Renal carcinoma (proven by radiography and examination of tumor following removal) | 2 |

a "doughnut" cell with peripheral cytoplasmic extrusions. The "budding" cell in Figure 2j exhibits a linear deposit of phase-dense material in the region of the cell membrane. A similar cell, much increased in size, is present in Figure 2k. Figure 2l contains the remnants of a cell, the membrane of which has ruptured, with a number of residual phase-dense cytoplasmic aggregates.

In contrast, red cells present in the urine as a result of bleeding into the renal pelvis, ureter, or bladder did not exhibit the range of morphologic variation seen above. The majority of cells had conventional morphology with apparently normal hemoglobin content, and the remainder were red cell "ghosts." (Fig. 3 shows red cells from the urine sediment of a patient with carcinoma of the bladder.) The proportions of relatively normal and "ghost" cells varied from patient to patient, and in addition crenated cells were present in some samples. In 9 of the patients with nonglomerular disease (3 with bladder polyps, 4 with carcinoma of the bladder, and 2 with renal carcinoma), red cells disappeared from the urine after the lesion was removed. In addition, 4 of the 9 patients with renal calculi had their stones removed surgically, and this was followed by resolution of the hematuria.

Figure 4 shows the urine red blood cell counts of 56 patients with glomerular bleeding. These provided a guide to the underlying lesion, in that most patients with only minor abnormalities on renal biopsy (including minimal lesion nephrotic syndrome) had low counts, whereas all urine samples from patients with focal and segmental proliferative lesions (frequently with cellular crescents) and those with mesangiocapillary glomerulonephritis yielded high cell counts.

The distribution of diagnostic groups in the patients with glomerular lesions set out in Fig. 4 is similar to that seen in a large series of patients with glomerulonephritis studied at this hospital [3]. Patients with microscopic hematuria and a normal urinary protein show the same distribution of lesions as do those with proteinuria and hematuria.

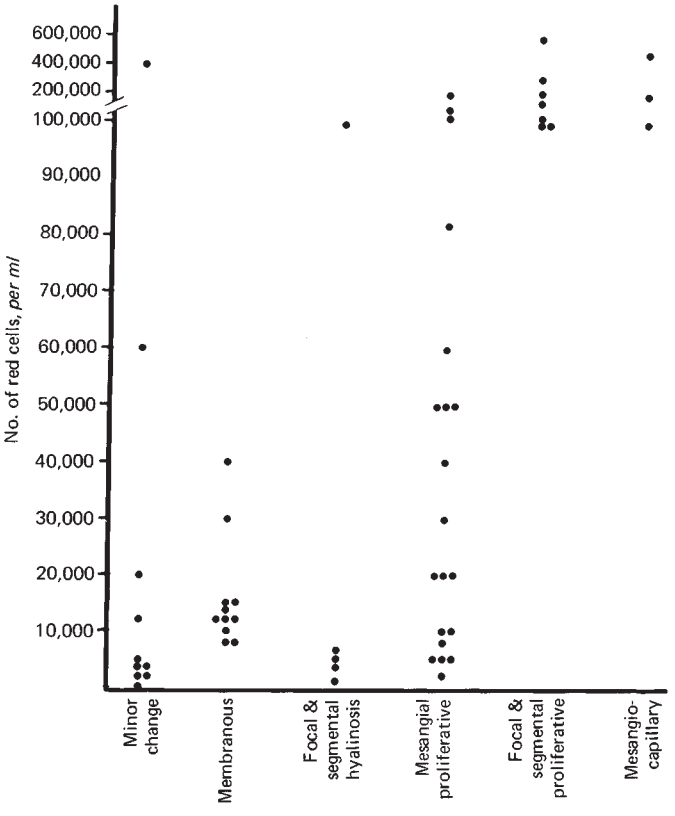


**Fig. 4.** *Urine red blood cell counts in patients with glomerulonephritis.*

## Discussion

These results confirm that glomerular bleeding is distinguishable from other causes of hematuria by phase-contrast microscopy of the urine sediment. Interestingly, Addis [4] observed dysmorphic red blood cells in urine samples from patients with glomerular disease, although he did not conclude that the presence of such cells in the urine was indicative of a glomerular lesion. The changes in red cell morphology described and illustrated in this report are obvious, and it should be feasible for the physician or laboratory scientist to suggest whether a glomerular lesion is likely to be present on the basis of a single urine examination.

Patients with dysmorphic red blood cells in the urine would

be further investigated with a view to assessing renal function and considering the advisability of a renal biopsy. Up to 20% of cells in 3 patients with mesangial IgA disease exhibited "non-glomerular" morphology. This led to a very careful search (including arteriography) for a nonglomerular cause of bleeding, which, however, was not found. IgA deposits have been reported in skin and muscle [5] and may be widespread in these patients. It is possible that similar vascular lesions might be present in the mucosa of the urinary tract, and this could account for some "nonglomerular" bleeding in this patient group. But patients with "nonglomerular" cells require the most careful evaluation because we have not seen these cells in the urine of the 200 healthy individuals examined to date. This is particularly important in the context of the present study in which only 2 patients with renal carcinoma were examined, and this lesion would require to be excluded in any patient with "nonglomerular" cells in the urine.

Patients with hematuria in whom dysmorphic red cells were not seen could be investigated by cystoscopy and, where necessary, further radiologic studies for a nonglomerular cause of hematuria. Red blood cells seen in the urine of healthy subjects are dysmorphic and may be present in numbers up to 8,000 cells/ml. For this reason, similar counts of "glomerular" cells in patients with "nonglomerular" bleeding are of no clinical significance.

At present, many patients with glomerular bleeding are subjected to unnecessary urologic and radiologic investigations. More selective use of these procedures would be possible if a search for dysmorphic red blood cells in the urine were undertaken at an early stage of patient investigation.

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