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Teaching Point
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How a skilful and motivated urinary sediment examination can save the kidneys

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Introduction

In many nephrological units, urinalysis is carried out only by dipstick, whilst urine sediment examination is entrusted to the personnel of central laboratories, far from the bedside of the patient and without the knowledge of the clinical features of the patients [1].

The following case shows the importance that urine sediment examination still has in clinical practice, when it is carried out by nephrologists experienced in the field.

Case

On 16 September 1997, one of us (FGB) examined by phase contrast microscope the urine sediment of an outpatient, whose urine by dipstick was positive for haemoglobin (+++) and albumin (+). Urine sediment contained 50–60 erythrocytes/high power field (HPF) of glomerular type, i.e. >5% acanthocytes [2], 3–5 leucocytes/HPF, >1cast/low power field (hyaline, granular, epithelial and erithrocytic casts) and 3–5 renal tubular cells/HPF, which were intermingled with several fragments of tubular epithelium (Figure 1).

These findings, which were those of a nephritic sediment associated with clear signs of severe tubular damage, led us to inquire further into the clinical features of the patient.

Thus, we attached a note to the urinary sediment report, in which we asked the patient to contact us as soon as possible. The day after, a boy arrived at our unit, who told us that the urine sample belonged to his father, who was under clinical evaluation for a right lumbar pain of recent onset. Worried by the severity of the urinary sediment findings, we asked the patient to supply a new urine sample and to check renal function.

The new urine sediment was the same as before. As in the previous sample, atypical uroepithelial cells indicating the presence of an urothelial malignancy, which in our patient might have explained the lumbar pain, were absent. These cells are characterized by irregular shape, enlarged and irregular nucleus, increased nuclear/cytoplasmic ratio, or increased number (>3) and/or size (>5 μm) of nucleoli [3]. Using phase contrast microscopy, we have been able to identify such cells in occasional patients, for whom our finding was always confirmed by cytological examination of the urine with Papanicolaou stain. Interestingly, these cells are very similar to the cells found in the urine of patients with polyomavirus BK infection [4], which we can also identify by phase contrast microscopy without the need for stains [5]. Proteinuria was 2.9 g/l, serum creatinine was 1.8 mg/dl (estimated GFR by Cockcroft–Gault formula 39 ml/min), while it was 1.1 mg/dl one month before.

Therefore, the patient was hospitalized in our unit. The clinical history was uneventful, and there was no history of drug use. The patient was without symptoms but for a mild right lumbar pain. Body mass index was 22 (normal value 18.5–25), blood pressure was 130/80 mmHg, heart rate was 76 beats/min. There were no signs of dehydration. At ultrasound, the kidneys were normal without stones, dilatations, or size increase, for which reason we hypothesized that lumbar pain was not of renal origin and was probably due to backbone spondyle-arthrosis. At this point, the patient underwent a renal biopsy.

The renal sample contained 21 glomeruli, three of which were globally sclerotic; three others showed segmental areas of fibrinoid necrosis (Figure 2A) and two others showed small cellular crescents. Numerous tubules were filled with erythrocytic casts (Figure 2B), while others showed degenerative changes of the

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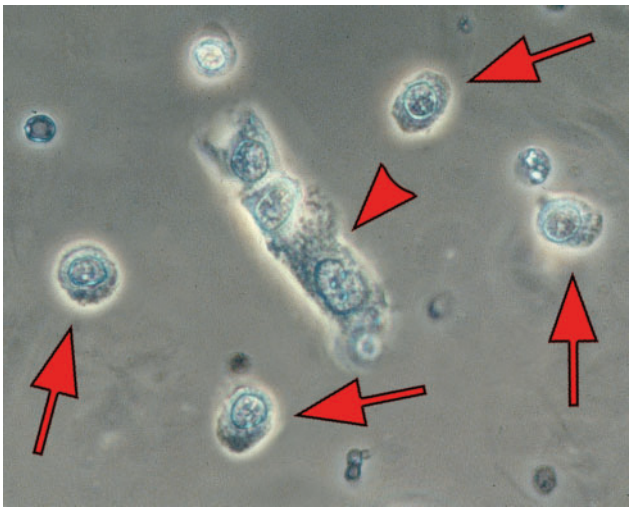

Fig. 1. Renal tubular cells (arrows) and a fragment of tubular epithelium (arrowhead)(phase contrast microscopy, original magnification × 400).

epithelium, associated with focal detachment of the cells from the tubular basement membrane (Figure 2C) and regenerative features, which were all indicative of an ongoing acute tubular necrosis. The interstitium showed a mild oedema and focal and mild mononuclear cellular infiltrate without tubulitis, while the vessels were normal. By immunoflourescence, only fibrinogen was found within the necrotic areas of glomeruli.

Due to the positivity for p-ANCA (anti-MPO immunoassay, Immunoscan Euro-Diagnostica, Malmö, Sweden), a diagnosis of p-ANCA-positive pauci-immune necrotizing GN associated with acute tubular necrosis was made, which was treated with three i.v. methylprednisolone pulses of 500 mg each, followed by oral prednisone (0.5 mg/kg/day) and oral cyclophosphamide (1.5 mg/kg/day).

At follow-up, there was a slow but progressive decrease of serum creatinine, with a progressive clearing of urinary abnormalities. In November 1998, 14 months after the diagnosis, serum creatinine was 1.1 mg/dl (estimated GFR 66 ml/min), and urinary sediment contained only 3–4 erythrocytes/HPF and occasional hyaline and hyaline-granular casts. Proteinuria was absent, while p-ANCA was still weakly positive. Treatment consisted of prednisone, 2.5 mg every other day.

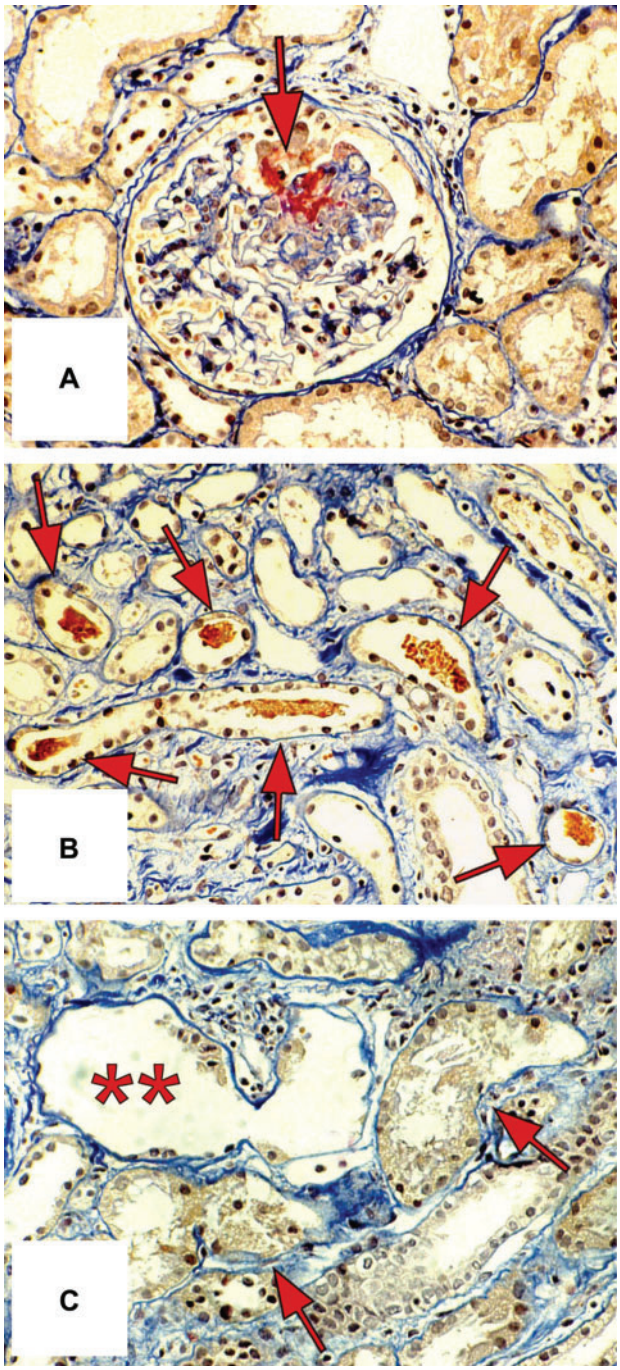

Fig. 2. (**A**) One of the three glomeruli with an area of fibrinoid necrosis (arrow); (**B**) Erythrocytic casts within the renal tubules (arrows); (**C**) A tubule showing the loss of a large portion of the tubular epithelium (**) and tubules showing severe degenerative changes of the epithelium (arrows)(AFOG stain, original magnification × 400).

Discussion

In our opinion, this case is interesting and educational for three reasons.

First, it shows that if the urine had been analysed only by dipstick, only the presence of haematuria and albuminuria would have been detected. The presence of erythrocytic casts, tubular cells and fragments of tubular epithelium would have been missed, findings which alarmed us and prompted the widening of the clinical investigation, which led to the diagnosis of an acute, severe and treatable renal disease.

It is important to retain the fact that dipsticks have other limitations besides the fact that they do

not detect important markers of renal disease such as casts [6], tubular cells, lipids and crystals.

Dipstick for haemoglobin, which is used to diagnose haematuria and is based on the pseudoperoxidase activity of the haeme moiety of haemoglobin, which catalyses the reaction of a peroxide and a chromogen to produce a coloured product, was found to have a sensitivity of 75% and a specificity of 88.6% when compared with microscopic examination of the urine sediment [6]. False negative results can be caused by concentrated or acidic urine and especially by the presence in the urine of variable amounts of ascorbic acid, which can lead to the non-diagnosis of low-grade microscopic haematuria [7]. On the other hand, false positive results occur especially for the presence in the urine of free haemoglobin (as seen in haemoglobinuria), myoglobin (as seen in marked muscle injury), or high concentrations of bacteria with pseudoperoxidase activity, such as *Enterobacteriaciae, Staphylococci and Streptococci* [8].

Dipstick for protein is based on the principle of the 'protein error', for which the presence of proteins in a buffer causes a change of pH which is proportional to their concentration. This method is sensitive to albumin (at a threshold of >250 mg/l), but it is much less sensitive to tubular proteins and light chain immunoglobulins [9]. In addition, it is only a semi-quantitative method, which allows only a rough quantification of urine albumin. For example, in a cohort of 30 patients with + albuminuria by dipstick (Combur Test, Roche Diagnostics, GmbH, Mannheim, Germany), we found that proteinuria, measured by red pyrogallol essay, ranged from 100 to 1600 mg/l (mean ± SD = 800 ± 300). These features can explain the discrepancy we found in our patient between proteinuria by dipstick (+) and proteinuria by red pyrogallol essay (2.9 g/l).

Second, if the urine sediment had been examined in a central laboratory, where tubular cells and various pathological casts often go unrecognized [10,11], once again the severity of the renal disease would have been missed, with serious consequences for the patient's health.

Third, this case clearly shows the close correlation which can exist between the intrarenal changes and the urinary sediment findings (Table 1). Thus, if fibrinoid necrosis and extracapillary proliferation, by causing the extravasation of erythrocytes within Bowman's space, are the causative mechanism of severe haematuria [12,13], the passage of erythrocytes into the tubular system and their entrapment within the matrix of forming casts, explains the finding of erythrocytic casts in the renal biopsy as well as in the urine. Finally, the damage of the tubular system, in this case secondary to the acute and severe glomerular damage, correlates well with the presence of tubular cells and tubular fragments in the urine [14].

Renal tubular cells can be found in a wide spectrum of renal disorders [15] (Table 2), and the presence (or absence) of other urinary sediment components can be of great help for a correct diagnosis. Thus, renal tubular cells associated only with 'muddy brown' granular casts and renal tubular cell casts suggest an ischaemic or nephrotoxic acute tubular necrosis [16], while the co-presence of non-glomerular haematuria, leucocyturia and leucocytic casts may give weight to a diagnosis of acute interstitial nephritis [17]. Tubular cells associated with moderate to severe dysmorphic haematuria, mild leucocyturia and erythrocytic cylindruria are suggestive of proliferative/necrotizing

Table 1. Correlations between renal biopsy and urinary sediment findings

Renal biopsy	Linking mechanisms	Urinary sediment
Glomerular necrosis/extracapillary proliferation	Extravasation of erythrocytes within Bowman's spaces and their passage into the tubules	Marked haematuria
Intratubular erythrocytic casts	Transport of casts by the intratubular stream through the tubular system	Erythrocytic cylindruria
Renal tubular epithelial damage	Sloughing of renal tubular cells within the tubular lumen	Renal tubular cells and tubular fragments

Table 2. Urinary sediment components which can be found in the urine in association with renal tubular cells and the associated clinical conditions

Urine components associated with renal tubular cells	Condition
'Muddy brown' granular casts and renal tubular cell casts	Ischaemic or nephrotoxic acute tubular necrosis
Non-glomerular erythrocytes, leucocytes (including oeosinophils in some instances) and leucocytic casts	Acute interstitial nephritis
Erythrocytes and erythrocytic casts	Proliferative/necrotizing glomerulonephritis
Fatty particles	Nephrotic syndrome

glomerulonephritis [18], while tubular cells associated with fatty components (fatty droplets, 'oval fat bodies', fatty casts, or cholesterol crystals) with few or no erythrocytes/erythrocytic casts are typical of nephrotic syndrome due to non-proliferative glomerular disorders [18].

Teaching points

(i) Urinalysis performed only by dipstick is inadequate for the evaluation of renal patients.
(ii) The examination of urinary sediments by a nephrologist experienced in the field has added value, compared with an examination carried out by personnel who do not know the clinical and pathological correlations of the urinary findings.
(iii) Therefore, in each renal unit there should be at least one nephrologist expert in the examination of urinary sediments.
(iv) The finding of a nephritic sediment and/or many renal tubular cells and tubular fragments should always suggest the presence of an active and severe renal disease and should prompt further action.
(v) A skilful and motivated urine sediment examination can save the patient from a progressive renal disease.

Conflict of interest statement. None declared.

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