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CASE REPORT

Acute renal failure in patients with glomerular diseases: a consequence of tubular cell damage caused by haematuria?

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ABSTRACT

We describe three patients with acute renal failure after the onset of gross haematuria. In all patients a presumptive diagnosis of rapidly progressive glomerulonephritis was made and immunosuppressive therapy initiated. A renal biopsy was performed in two patients, which showed evidence of IgA nephropathy. Extracapillary proliferation was seen in a few glomeruli. The most notable abnormality was acute tubular necrosis with intraluminal erythrocytes and cell debris. In the third patient, who was known to have longstanding glomerular haematuria, acute tubular necrosis was considered likely after review of the urinary sediment. Despite the fact that immunosuppressive therapy was stopped, renal function rapidly returned to normal in all these patients. We feel that our patients and additional literature data demonstrate that in patients with glomerular disease a reversible acute renal failure can occur that is caused by acute tubular necrosis mediated by haematuria. Recognition of this entity will prevent unnecessary long-term immunosuppressive therapy.

INTRODUCTION

The nephritic syndrome is characterised by haematuria, oliguria, hypertension and often progressive renal failure. In most patients the underlying cause is a glomerulonephritis. Well-known examples are the extracapillary (crescentic) glomerulonephritis in patients with a systemic vasculitis or anti-GBM disease and the endocapillary proliferative glomerulonephritis after a streptococcal infection. In the former group of patients immunosuppressive treatment must be started without delay to ensure recovery of renal function. Therefore, in many patients immunosuppressive therapy is started at the moment that an extracapillary glomerulonephritis is suspected, often before renal biopsy findings are available.

It is not well known that patients with macroscopic glomerular haematuria may develop a reversible acute renal failure due to acute tubular necrosis, which is attributed to haemoglobin-mediated tubular cell injury. We present three patients to demonstrate the clinical picture.

CASE REPORT 1

A 63-year-old woman with hypertension (150/100 mmHg, ventricular response 100 beats/min) and atrial fibrillation was admitted to the hospital because of vasculitic skin lesions. During the admission she developed proteinuria and renal insufficiency. Physical examination revealed hypertension, and red and purple skin lesions. Diuresis amounted to 600 ml/day, and her urine was stained dark brown, compatible with macroscopic haematuria. The urinary sediment showed more than 50, mostly dysmorphic erythrocytes per high power field, and numerous red cell casts, which are virtually diagnostic of glomerulonephritis. Additional laboratory analysis (antinuclear antibodies (ANA), antineutrophilic cytoplasmic antibodies (ANCA), anti-GBM antibodies, cryoglobulins, and complement profile) was unremarkable. A renal biopsy disclosed a focal extracapillary glomerulonephritis. On immunofluorescence IgA deposits were seen in the mesangium and to a lesser extent in the capillary loops. These clinical and histological findings supported a diagnosis of Henoch-Schönlein

purpura with renal involvement. Given the progressive nature of the renal insufficiency, therapy with prednisone and cyclophosphamide was instituted. The clinical course (*figure 1*) was complicated by traumatic hip fracture and urinary tract infections. After an initial recovery of renal function the serum creatinine rose again. A second opinion was sought and the renal biopsy was revised. In the biopsy 55 glomeruli where present, 15 of which showed signs of recent extracapillary inflammation. Most remarkable, however, were signs of extensive tubular cell damage and tubular cell necrosis (*figure 2A*) and erythrocytes in the tubuli (*figure 2B*). The histological findings confirmed that the patient was suffering from a glomerulonephritis with IgA deposits, in the context of Henoch-Schönlein purpura. However, it seemed unlikely that the glomerular abnormalities could fully explain the renal insufficiency and we assumed that the acute tubular necrosis, so predominantly present, was the cause of the renal insufficiency and that there was no indication for immunosuppressive therapy. The treatment with prednisone and cyclophosphamide was stopped. The further clinical course was complicated by the development of acute congestive heart failure with further deterioration of renal function (*figure 1*). Eventually there was a near complete recovery of renal function.

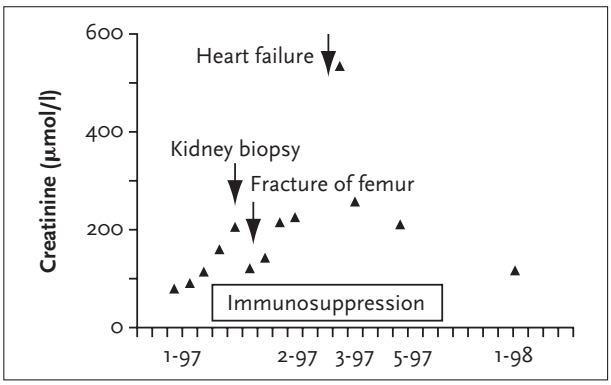

Figure 1
Time course of serum creatinine in patient 1

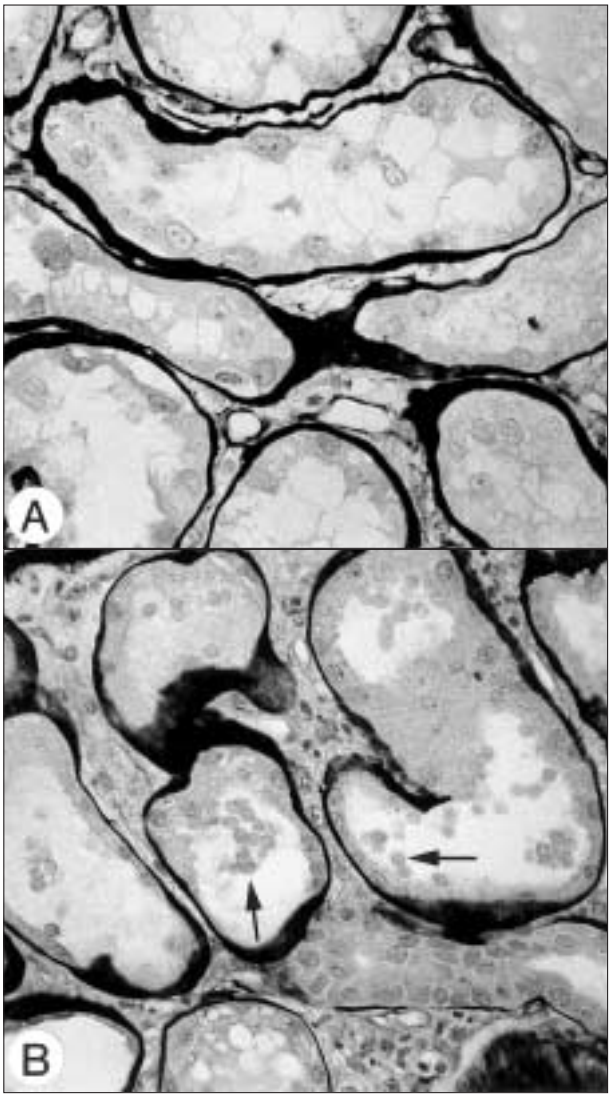

Figure 2
Light microscopy of the kidney biopsy in patient 1
There is evidence of extensive necrosis and injury of the tubular epithelial cells (panel A). Tubular cells have disappeared or detached from the tubular basement membrane and there is evidence of cell and nuclear activation. Panel B shows erythrocytes filling the tubular lumina (arrows). (Methenamine silver-staining, A 400x, B 400x.)

CASE REPORT 2

A previously healthy, 36-year-old woman developed a sore throat and fever. One day later she consulted the family physician, who prescribed a penicillin antibiotic. The same day she noticed that the urine production had diminished and that it was stained dark brown (tea-colour). On the third day she was admitted to a hospital and because of progressive renal failure she was transferred to our hospital two days later. On admission the blood pressure was 145/95 mmHg, with a pulse rate of 64 beats/min. The pharynx was red with inflamed tonsils. There was no oedema present. Laboratory values on admission were: creatinine 729 µmol/l, urea 15.3 mmol/l, C-reactive protein 157 mg/l, anti-streptolysin titre normal, anti-DNase B was elevated, ANA negative, ANCA negative, complement C3 and C4 normal. Urinalysis showed gross haematuria, in which it was not possible to discern the morphological aspects of the erythrocytes. Renal function and urinary output progressively declined (*figure 3*). Renal biopsy was not feasible due to a prolonged bleeding time. Since an extracapillary glomerulonephritis as cause of the progressive renal failure could not be ruled out immunosuppressive therapy with steroids was instituted. Haemodialysis was started. After normalisation of the bleeding time a renal biopsy was performed 10 days after onset of the haematuria. In the biopsy 15 glomeruli were present, and 5 glomeruli showed

signs of extracapillary proliferation. On immunofluorescence there were discrete mesangial IgA deposits. There was evidence of tubular damage, and in some tubules erythrocytes and cellular debris from necrotic cells were present (*figures 4A* and *4B*). We concluded that the patient had IgA nephropathy, presenting with gross haematuria after an upper respiratory tract infection. Renal failure was thought to have developed as a consequence of tubular cell damage. Immunosuppressive therapy was rapidly decreased and stopped. The further clinical course was uneventful (*figure 3*) and renal function completely normalised. Outpatient follow-up showed that there was residual albeit very slight proteinuria. The urinary sediment persistently showed some dysmorphic erythrocytes.

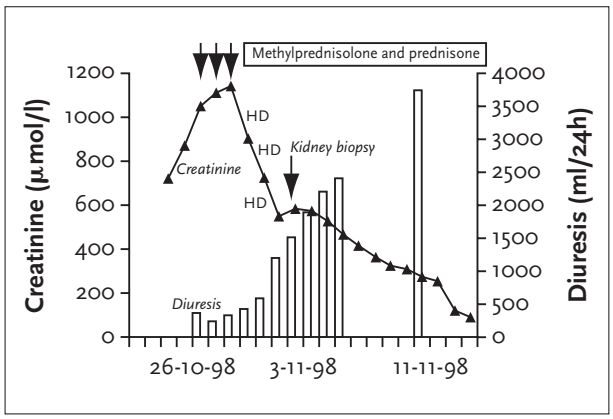

Figure 3
Time course of renal function and diuresis in patient 2

CASE REPORT 3

A 36-year-old woman was known with haematuria from her youth. The urinary sediment at that time showed many dysmorphic erythrocytes and erythrocyte casts. Renal function was normal and there was no proteinuria or hypertension. Benign glomerular haematuria was diagnosed, possibly as a consequence of IgA nephropathy. She now presented with a three-day history of fever, a sore throat, headache, nausea and vomiting. A physician had prescribed Pheneticillin. The day after onset of the fever, her urine was stained dark and the urinary output was reduced. On physical examination she did not appear acutely ill. The blood pressure was 140/75 mmHg and the pulse 76 beats/min. Further examination was unremarkable, no oedema was present. The serum creatinine was markedly elevated (682 µmol/l). Urinary sodium was 32 mmol/l, the urinary sediment showed 20 to 50 mostly dysmorphic red blood cells per high power field with red cell casts. On ultrasound examination the kidneys were normal without outflow obstruction. Since a rapidly progressive renal failure due to extracapillary glomerulonephritis was considered possible, i.v. methylprednisolone and oral cyclophosphamide were started. On the following day the urinary sediment further revealed many granular casts and tubular epithelial cells. The urinary output seemed to increase. As the sediment was compatible with acute tubular necrosis and in view of the absence of hypertension and sodium retention, immunosuppresive therapy was stopped. The clinical course was uneventful with a complete recovery (*figure 5*).

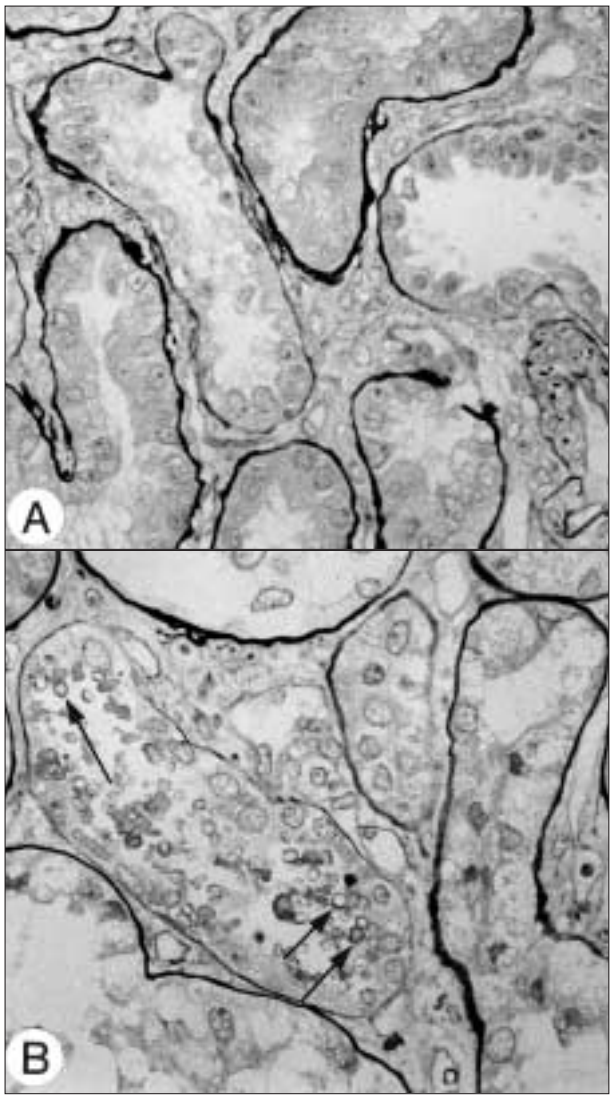

Figure 4
Tubular cell injury in the kidney biopsy of patient 2
There are signs of cell and nuclear atypia (panel A). In some tubuli erythrocytes can be recognised between granular debris (arrows) (panel B). (Methenamine silver-staining, A 400x, B 400x.)

DISCUSSION

We describe three patients who developed acute renal failure during a period of gross haematuria. In two patients a definite diagnosis of IgA nephropathy was made, in patient 3 a diagnosis of IgA nephropathy was very likely given the

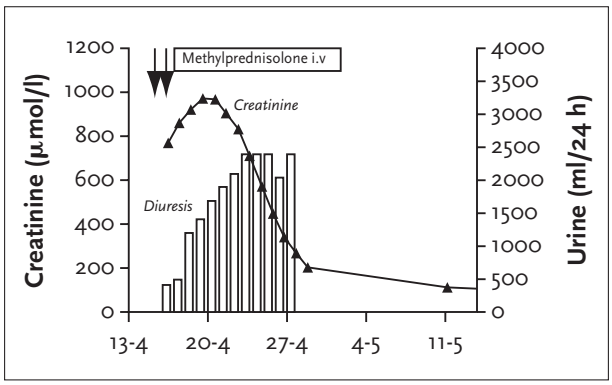

Figure 5
Time course of renal function and diuresis in patient 3

medical history. It is well known that patients with IgA nephropathy frequently experience periods of macroscopic haematuria that are often provoked by fever, infection or exercise. Typically there is a short interval of hours or days between the provoking factor (e.g. an upper respiratory tract infection) and the appearance of haematuria. In contrast, in postinfectious (poststreptococcal) glomerulonephritis the interval between the infection and the occurrence of haematuria ranges from 10 to 21 days.

In patients with renal failure the presence of dysmorphic erythrocytes and red cell casts is virtually pathognomonic for the presence of glomerular lesions. It is therefore almost inevitable that the glomeruli receive the most attention on histopathological examination of the renal biopsy. In two of our patients evidence of an IgA nephropathy was found in the glomeruli. In 25 to 30% of the glomeruli, extracapillary proliferation was present. The presence of extracapillary proliferation points to serious damage of the capillary wall, often with necrosis. An extracapillary glomerulonephritis is most often associated with a vasculitis. However, it is well known that in many forms of primary glomerulonephritis, some glomeruli show extracapillary proliferation. In patients with IgA nephropathy extracapillary proliferation is found in 17% of the patients and in 5 to 50% of the glomeruli.[1] Signs of extracapillary proliferation are found more often in periods of macroscopic haematuria. It is very important that one realises that renal insufficiency per se cannot be ascribed to the presence of a small number of glomeruli with signs of extracapillary proliferation. In anti-GBM disease or vasculitis with rapidly progressive renal failure (serum creatinine >500 µmol/l) crescents are found in at least 50% and usually in more than 80% of the glomeruli.[2,3]

In our patients the renal biopsies showed signs of tubular cell damage (case report 1). In case report 2 the pathological abnormalities of the tubular apparatus were less noticeable, which can be explained by the fact that the biopsy was taken late after the onset of haematuria, in the recovery phase.

In case report 3 the urinary sediment findings were highly suggestive of acute tubular necrosis. Furthermore, in this case, there were no other signs of the nephritic syndrome such as hypertension, oedema or urinary sodium retention. Acute renal failure caused by macroscopic haematuria has been described previously in patients with IgA nephropathy.[4-6] The renal failure is thought to be caused by the erythrocytes in the tubuli and attributed to either intratubular obstruction or a direct toxic effect on the tubular epithelial cells by haemoglobin or iron. Alternatively, we cannot exclude that cytokines produced by the inflammatory cells may contribute to the development of tubular cell injury. In all circumstances it is likely that volume depletion will enhance the risk of developing acute renal failure.

The incidence of renal failure caused by haematuria is probably high, although it is often overlooked and not recognised. In a prospective study in which the occurrence of renal failure during episodes of macroscopic haematuria was studied, 11 of 29 patients developed renal failure.[4] The mean serum creatinine was 271 µmol/l, (108-603 µmol/l), the maximal value being reached three to ten days after the onset of haematuria. Renal function normalised in all cases, although the time needed for recovery varied from 15 to 70 days. Renal biopsies taken within four days after the onset of haematuria showed considerable tubular cell damage, with erythrocyte casts in most of the tubuli. Extracapillary proliferation was noticed in 3 to 15% of the glomeruli. A striking finding was that in late biopsies, taken 12 days after the onset of haematuria, there was only mild tubular damage and that hardly any erythrocytes could be found in the tubular lumina. Other authors have largely confirmed these findings.[5,6] In some of the patients reported in the latter studies renal insufficiency was so severe that haemodialysis was necessary. The number of crescents found in renal biopsies varied between 0 and 37%. In almost all cases renal function recovered.

Acute renal failure due to haematuria has also been described in patients with other forms of glomerulonephritis.[7] Notably, in one paper acute renal failure was described in a marathon runner, who developed haematuria shortly after finishing the race. The renal biopsy did not disclose any glomerular abnormality, but erythrocyte casts filled the tubular lumina.[8]

In our patients we cannot formally exclude that the short-term use of immunosuppressive therapy contributed to the improvement of renal function. However, most patients with extracapillary glomerulonephritis do not respond to short-term (days) prednisone therapy. Furthermore, even the most vigorous treatment with steroids, cyclophosphamide and plasmapheresis mostly results in a slow improvement of renal function, with clear evidence of renal failure being still present two months after the start of treatment.[9] These findings are in sharp contrast with the course of renal recovery in our patients.

In conclusion, patients with glomerular diseases and macroscopic haematuria may develop acute renal failure due to tubular necrosis. In a patient with rapidly progressive glomerulonephritis and macroscopic haematuria the absence of hypertension and oedema, and an increased urinary sodium concentration must raise suspicion to include acute tubular necrosis in the differential diagnosis. In these patients volume depletion must be vigorously treated. The recognition of this entity is of importance as it prevents the institution and maintenance of potentially harmful immunosuppressive therapy.

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