Acute renal failure in IgA nephropathy: Aggravation by gross hematuria due to anticoagulant treatment

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ABSTRACT: IgA nephropathy is one of the most common forms of glomerulonephritis. Macroscopic or microscopic hematuria with mild proteinuria are the main symptoms. Without complicating factors, IgA nephropathy has a favourable long-term prognosis. We report a case of reversible acute renal failure (ARF) as a complication of mild IgA nephropathy while oral anticoagulants were administered. Diagnosis was based on a renal biopsy showing marked granular mesangial IgA-deposition. In addition, numerous tubules were extended and completely obstructed by red blood cell casts. After hemodialysis treatment and parallel anti-inflammatory steroids and after stopping anticoagulation, renal function gradually improved up to complete remission. This report indicates that anticoagulatory treatment may have negative effects on the long-term prognosis of IgA nephropathy with respect to development of ARF or tubulo-interstitial inflammation.

Key words: IgA, Nephropathy, Acute renal failure, Anticoagulants

Introduction

In the pathogenesis of acute renal failure (ARF) associated with chronic glomerular diseases, tubular obstruction by red blood cell or proteinuric casts is considered of pathogenic relevance. Although this is an unusual complication, worsening of renal function was described in IgA nephropathy during episodes of macroscopic hematuria (1). The formation of erythrocyte casts may lead to peritubular-interstitial inflammation and obstruction of urinary flow. These pathophysiological mechanisms may be aggravated by effective anticoagulatory treatment. This assumption is supported by the present case, in which a woman developed reversible ARF as a complication of mild IgA nephropathy, while taking oral anticoagulants. IgA nephropathy is one of the most common forms of glomerulonephritis in adolescents and adults worldwide. Clinically it presents with macroscopic or microscopic hematuria in conjunction with mild proteinuria (2). Unless aggravated by hypertension, heavy proteinuria or impairment of function, IgA nephropathy has a favourable long-term prognosis (3). There are, however, reports of ARF in cases of isolated IgA nephropathy (4,5) or in IgA nephropathy associated with HIV infection (6) or Crohn's disease (7). Since the glomerular lesions were in most cases too mild to account for ARF (8), both glomerular and tubular lesions have been suspected as...
leading to the loss of renal function (9-11).

Case report

A 59-year old woman was admitted to hospital with fatigue, drowsiness and edema of her ankles. Two days before admission she had had dyspnea and vomiting. She reported having macrohematuria for 14 days without any dysuria, fever or flank pain. She had a long history of hypertension and was on oral anticoagulants (phenprocoumon) because of a deep venous thrombosis of the left leg three months earlier. Underlying hemostatic disorders were excluded by extensive laboratory testing. Apart from a thyroidectomy, years before, she had no other noteworthy medical problems. She had no family history of congenital or acquired kidney diseases.

She presented with mild dyspnea and pitting edema of her ankles. Blood pressure was 120/80 mmHg, pulse rate 80/min and body temperature within normal limits. Other physical findings, including skin, lung, abdomen, joints and reflexes were also normal. Her chest X-ray and electrocardiogram were normal.

Laboratory tests gave the following values: hematocrit 28.9%, hemoglobin 9.4 g/dL, normal white blood cell count and platelets; serum creatinine 12.4 mg/dL; serum nitrogen urea 132 mg/dl; uric acid 10.7 mg/dL; phosphate 11.2 mg/dL; normal findings for sodium and potassium. PPT was 21s, INR 3.2. All other routine blood examinations were normal, including serology for hepatitis B and C, HIV, and tests for antinuclear antibody (ANA), anti dsDNA and rheumatoid factor; C-reactive protein was negative. Urinalysis revealed proteinuria of 75 mg/dL, more than 30 red blood cells (RBC) and 10 to 15 white blood cells (WBC) per field. Abdominal ultrasonography disclosed no evidence of renal vein thrombosis, urolithiasis, or postrenal stenosis. Because rapid anuria developed, renal biopsy was done under ultrasound guidance after normalising coagulation. The renal tissue was routinely examined and submitted to a triple diagnostic procedure including immunohistochemistry and electron microscopy.

Conventional light microscopy showed only minor widening of the mesangial matrix and a capsular connection was detectable in a single glomerulus. Immunohistochemistry (Fig. 1A) indicated marked granular mesangial IgA-deposition. Therefore the patient was diagnosed as having IgA nephropathy. No significant cellular proliferation or crescentic lesions were seen. Ultrastructurally, mesangial osmiophilic depots were observed with corresponding complexes containing IgA. Immunohistological methods showed little complement (C3) activation. Immunohistochemistry detected no deposition of IgG.

As shown in Figures 1B and 1C, numerous tubules were extended and completely obstructed by RBC casts. Marked siderin storage was observed in the corresponding tubular epithelial cells and in some peritubular macrophages too. Proximal tubular cells were in part flat and had a loss of microvillose border. There was no tubular cell necrosis. Mild interstitial edema infiltrated by a small number of lymphocytes and histiocytes was accumulated in peritubular regions (Fig. 1D). This was sometimes accompanied by fibroblasts but not by fibrous connective tissue.

ARF was assumed to be a consequence of renal bleeding due to the anticoagulation and hemodialysis was necessary. After ten hemodialysis sessions, and after stopping anticoagulation, renal function gradually improved (Fig. 2). Treatment was paralleled by pulse steroid therapy because of acute deterioration of renal function and to prevent IgA production. This was also administered because the marked siderin storage caused high inflammatory activity. The pulse therapy did not follow any specific scheme but was adapted to the clinical course. After one month, creatinine, serum nitrogen urea and urine analysis showed normal results.

Fig. 1 - Light microscopy picture of renal bioptic tissue.
1A: Immunohistochemical demonstration of mesangial granules of IgA (APAAP, detected by neufuchsin, 500 x); no evidence of mesangial or capsular epithelial cell proliferation.
1B: Marked tubular obstruction by red blood cell casts (Masson-Goldner, 100x).
1C: Moderate iron storage within proximal tubular cells. Note also some siderin loaded peritubular macrophages ("Prussian blue", 400 x).
1D: Peritubular mild interstitial edema with some inflammatory and fibroblastic cells (PAS, 250 x).
Fig. 2 - Clinical course of the patient, a 59-year-old woman.

Discussion

This case was special because ARF in IgA nephropathy is a rare complication, with a frequency of 3% (13). Crescents are found in less than 1% of patients. Crescentic glomerular lesions, severe enough to account for the impairment of renal function, are observed only in unusual situations such as HIV-associated IgA nephropathy (6).

The association of tubular RBC casts with a gross hematuria is consistent with a prospective study showing worsening of renal function during episodes of macroscopic hematuria (1). IgA nephropathy is of course characterised by hematuria but here it was aggravated by anticoagulation. Monosymptomatic cases with isolated hematuria have a favourable long-term prognosis, unless associated with proteinuria, hypertension or functional impairment (2). About one third of patients with IgA nephropathy reach end-stage renal disease after 20 years.

In this patient ARF developed ten days after the occurrence of gross hematuria due to IgA nephropathy. Most probably, the oral anticoagulation for deep vein thrombosis had aggravated the hematuria. Kidney biopsy examination showed only mild glomerular alteration, without segmental necrosis or crescents, suggesting that tubular, not glomerular injury was responsible for ARF. Although the pathogenesis of ARF is not completely understood, the results support the importance of tubular obstruction in non-crescentic glomerular diseases complicated by ARF. Patients suffering from glomerulonephritis with ARF had a significantly higher incidence of macroscopic hematuria and RBC casts in the tubules (8,14). The tubular lesions were considerable and consisted of tubular necrosis, erythrocyte casts, erythrocyte phagocytosis by tubular cells accompanied by
interstitial edema, RBC extravasation, and interstitial inflammation (15). However, all alterations and the loss of function were usually completely reversible. Tubular necrosis was absent in our case and the tubular RBC casts were the most obvious light microscopy finding. Peritubular interstitial edema or cytotoxic effects of siderin as a consequence of siderin uptake and storage in peritubular cells could be causative factors. In liver diseases, the toxic effects of iron after cell overloading is a well-characterised pathological mode of cellular injury (12). Similar to liver cells, therefore, cytotoxic effects of iron on kidney tubules might induce peritubular fibrosis over a long time. It is possible that iron accumulation in endolysosomes has a signal function for vasoactive and inflammatory genes inducing up-regulation of activated TGFβ as a progression factor in almost all renal diseases and, possibly, by the transformation of monocytes and mesenchymal progenitor cells into fibroblasts.

If coagulation is impaired, for example by treatment with anticoagulants, glomerular lesions may be aggravated by tubular damage mediated by increased hematuria. Nevertheless, in some Japanese studies, treatment of IgA nephropathy in childhood including anticoagulants such as heparin-warfarin, and immunosuppressive agents, prevented the increase of sclerosed glomeruli (16). Many studies with small numbers of patients indicate that long-term treatment of IgA nephropathy with anticoagulants alone may slow loss of renal function (17).

In conclusion, the positive effects of anticoagulation in long-term treatment of IgA nephropathy need to be clarified, anticoagulation may be one of the main risk factors for the development of ARF in patients with microhematuria. This is important today as life expectancy increases, and cardiovascular complications in older age, for instance, may call for oral anticoagulation. In younger patients with microhematuria and thrombophilia, oral anticoagulation must be administered very carefully because although it may be necessary to deal with coagulation disorders it may have serious consequences due to unexpected ARF.

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