

A case of crescentic IgA nephropathy treated with prednisolone and cyclophosphamide

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Abstract

IgA nephropathy (IgAN) is the most common glomerulonephritis in the world, and currently is known to be an important cause of end stage renal disease (ESRD). Hypertension, proteinuria more than 1 g/d, and the presence of severe lesions on initial renal biopsy such as crescents and interstitial fibrosis are the most significant predictive factors for progression to ESRD. Despite its prevalence and clinical importance, there is no consensus for the treatment of patients with risk factors for a worse prognosis. Our aim is to describe here a case of crescentic IgAN, and to emphasize the effect of immunosuppressive treatment. Hippokratia 2009; 13 (3): 172-174

Key words: IgA nephropathy, crescents, proteinuria, immunosuppression

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IgA nephropathy is the most common glomerulonephritis diagnosed in renal biopsies¹. The most typical presentation is macroscopic hematuria shortly after a mucosal infection such as upper respiratory tract infection and bronchitis. Patients rarely present with nephrotic syndrome. It is now well-known that prognosis is highly variable with some patients showing a rapid progression, and IgAN has been an important cause of end stage renal disease (ESRD)². Factors including male gender, persistent microscopic hematuria, increased serum creatinine, proteinuria more than 1 g/d, and hypertension at presentation are associated with a worse outcome. On biopsy, crescents, global or segmental sclerosis, tubular atrophy, interstitial fibrosis, interstitial cellular infiltrate, and peripheral capillary wall alterations such as deposits or endocapillary proliferation also indicate a poor prognosis³. There is no consensus among authors for treatment of patients at risk for progression. Although some of them have advocated supportive treatment, others have recommended immunosuppressive treatment for patients who have rapidly progressive renal failure with more than 50% crescents and/or glomerular necrosis in the biopsy⁴. We report here a case of crescentic IgAN who had risk factors for progression, which improved with immunosuppressive treatment.

Case Report

A 21 year old man was referred to our nephrology department because he had microscopic hematuria and 2 + proteinuria on urinalysis during his routine military examination. He had macroscopic hematuria beginning at the same time with an upper respiratory tract infection three weeks ago, which subsided in a few days. He had

no other significant past medical history. On admission, blood pressure was 120/80 mmHg, pulse rate was 84/min while body temperature was normal. Body mass index (BMI) was 21.5 kg/m². His physical examination was unremarkable.

Laboratory tests showed hemoglobin: 14.2 g/dl, hematocrit: 37 %, white blood cell count: 7800/μl, platelet count: 286,000/ μl, blood urea nitrogen (BUN): 19 mg/dl, creatinine: 132 μmol/l, albumin: 3.3 g/dl, cholesterol: 181 mg/dl, triglyceride: 80 mg/dl, LDL-cholesterol: 115 mg/dl. Serum electrolytes were within normal limits. Urinalysis showed 3+ proteinuria by dipstick, and 8 red cells per high power field. Urinary protein excretion was 6.5 g/24h. P-anti neutrophil cytoplasmic antibody (P-ANCA), C-anti neutrophil cytoplasmic antibody (C-ANCA), anti-nuclear antibody (ANA), and anti-double stranded DNA (dsDNA) antibody, anti- glomerular basement membrane (GBM) antibody were negative. Serum complement levels (C3, C4) were normal. Screening for hepatitis B, hepatitis C and HIV (human immunodeficiency virus) was negative. Chest radiography was normal. On ultrasonography, both kidneys were of normal size, but increased parenchymal echogenicity. Renal biopsy was performed and is shown in figure 1A. On light microscopy, diffuse mesangial and endocapillary hypercellularity in all the glomeruli whereas in 14 of 24 glomeruli (58%) crescents (9 fibrous/fibrocellular and 5 cellular) were established. Most glomeruli exhibited periglomerular inflammation and the tubules were atrophic in fibrotic areas. The rest of tubules demonstrated regenerative changes.

There were moderate mononuclear infiltrations and mild fibrosis in interstitium. Fibrinoid necrosis of few arterioles were also noted. Immunofluorescence micros-

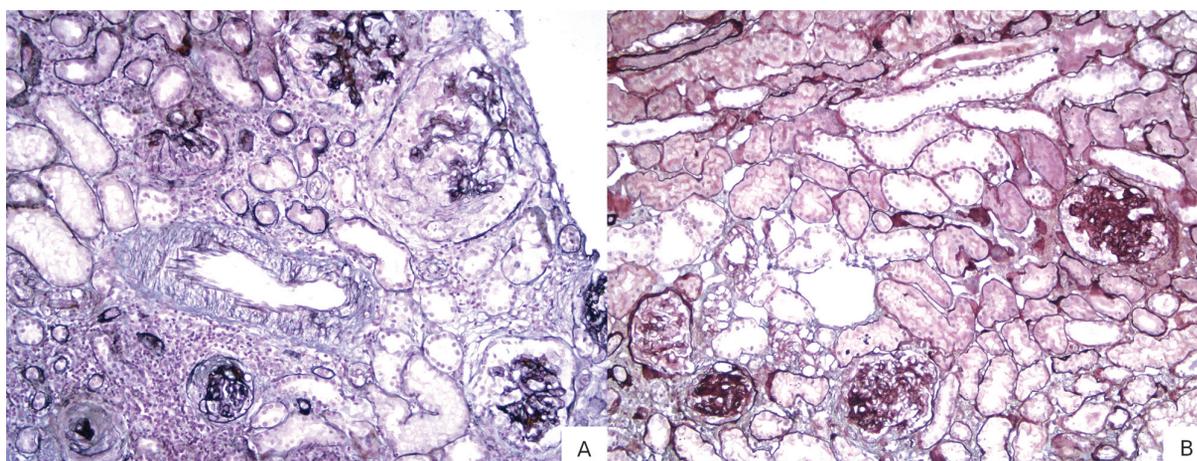


Figure 1A: Pretreatment light microscopy showing crescentic glomerulonephritis (JMSx200)

Figure 1B: Posttreatment renal biopsy findings (JMSx200)

copy showed a coarse granular deposition of IgA (3+), C3 (3+), and IgM (2-3+) in the glomeruli, mesangium and tubules. A diagnosis of crescentic IgAN was established. Treatment was initiated with intravenous pulse methylprednisolone (500 mg/d) for three days followed by tapering dose of oral prednisolone and monthly intravenous cyclophosphamide at 0.5 g/m² body surface area for three months followed by azathioprine (1.5 mg/kg/d). Serum creatinine was 105.6 µmol/l, and urinary protein excretion was 3 g/d. Two months later a renal biopsy was repeated and crescents were only seen in 7 of 34 glomeruli (21 %). There were no differences in tubulointerstitial findings (Figure 1B). Laboratory analysis revealed urinary protein excretion 2 g/d, 2.2 g/d, and serum creatinine 105.6 µmol/l, 96.8 µmol/l at the third and tenth months of treatment respectively. Microscopic hematuria persisted during the follow-up. His blood pressure was often 120/80 mmHg or less.

Discussion

Although IgAN is primarily characterized by mesangial IgA deposition, light microscopic appearances and clinical features of patients can vary considerably. Proliferative and crescentic forms of IgA are associated with nephrotic-range proteinuria. IgAN is a disease that may lead to ESRD. Approximately 25 to 30% of patients require renal replacement therapy within 20 to 25 years^{5,6}. Hypertension, severity of proteinuria, and the presence of severe lesions on initial renal biopsy such as hyalinosis, and crescents are the most predictive factors for progression to ESRD².

Dais et al retrospectively analyzed data from 144 patients with IgAN. They concluded that crescents were associated with an increased initial serum creatinine, proteinuria, hypertension and progression to ESRD⁷. Reich et al revealed that the rate of GFR decline was significantly slower in patients with proteinuria <1 g/d than in those with proteinuria >1 g/d, and proteinuria was the most important predictor of the rate of GFR decline⁸.

Despite its prevalence and clinical importance, there is no consensus for the treatment of patients with risk factors for a worse prognosis. The renoprotective effects of angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) are well-known, but it has been recommended that these drugs should not be used alone in IgAN patients with poor prognostic factors⁶.

In a study conducted by Hogg et al, it was found that alternate day prednisone or omega-3 fatty acids was not superior to placebo in slowing progression of renal disease⁹. In another study, a low dose of prednisolone had an antiproteinuric effect. However, it could not improve renal survival¹⁰. Nonetheless, there are a number of studies suggesting that steroids and/or cyclophosphamide reduce proteinuria and preserve renal function. Pozzi et al assessed the efficacy and safety of a 6 month course of steroids in IgAN. In that study, they found that the deterioration in renal function was less in the treatment group than in the control group ($P < 0.048$), and that proteinuria was significantly decreased ($P < 0.05$)¹¹. The same authors also reported that ten years renal survival in patients treated with steroids for 6 months was better than in the control groups ($P = 0.0003$)¹².

Tumlin et al investigated clinical and histological response to methylprednisolone and intravenous cyclophosphamide in patients with crescentic, proliferative IgAN, and found significant decreases in serum creatinine and proteinuria. Furthermore, they established that endocapillary proliferation, cellular crescents and karyorrhexis were eliminated in all the patients. In that study, ESRD was developed only in one of 12 patients after 36 months¹³.

Ballardie et al showed that immunosuppressive treatment with steroid and cyclophosphamide significantly preserved renal function during the follow-up lasting 2-6 years¹⁴.

Our patient had many poor prognostic factors including male gender, nephrotic proteinuria, renal impairment,

and severe microscopic findings at the time of diagnosis. However, treatment with prednisolone and cyclophosphamide reduced proteinuria from 6.5 g/d to 2.2 g/d and decreased serum creatinine from 132 $\mu\text{mol/l}$, to 96.8 $\mu\text{mol/l}$. We showed obvious regression of crescents on the light microscopy. Furthermore, we did not observe any side effects associated with treatment.

In conclusion, although prospective studies comparing immunosuppressive treatment with supportive one are warranted, we believe that immunosuppressive treatment is useful in IgAN patients with poor risk factors for progression.

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