The Curious Case of Crescentic IgA Nephropathy

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Immunoglobulin A Nephropathy (IgAN) is recognized to be the most common cause of primary glomerulonephritis. The classic presentation is macroscopic hematuria; however, the presentation may vary. The progression of IgAN to either chronic kidney disease or end-stage renal disease requiring renal replacement therapy is variable and subject to several clinical and histopathological factors.

We report a case of crescentic IgAN, a rare variant of IgAN, in a fifty-five-year-old Bahraini male who has had multiple risk factors for end-stage renal disease, yet showed significant improvement on immunosuppressive treatment.

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IgA deposits in the glomerular mesangium and produces an array of clinical presentations, from mild mesangial hypercellularity and asymptomatic microscopic hematuria to the crescent formation and rapidly progressive glomerulonephritis[1]. It usually affects children and young adults, but it could affect the elderly[2].

Poor prognostic factors in IgAN have been recognized as male predominance, refractory hematuria, proteinuria of more than 1g/dL and hypertension. Some histopathological findings have also been associated with poor outcomes, some of which include crescents, sclerosis, tubular atrophy and interstitial fibrosis[3].

Rapidly progressive renal glomerulonephritis is uncommon in IgAN, less than 5%. It can develop as an acute severe immune and inflammatory injury creating crescents or it can develop as crescents superimposing on a known milder IgAN, both of which are known as crescentic IgAN[1].

The aim of this report is to present a case of crescentic IgAN, a rare variant of IgAN who showed significant improvement on immunosuppressive treatment.

THE CASE

A fifty-five-year-old Bahraini male, hypertensive controlled with carvedilol, amlodipine, and irbesartan/hydrochlorothiazide, presented with painless hematuria and worsening renal function associated with weight loss.

Four months before admission, the patient had normal renal function, a serum creatinine baseline of 73 mmol/L. His deteriorating renal function was found incidentally during pre-operative assessment for cystoscopy.

The systolic blood pressure ranged between 150-180, serum creatinine of 393 mmol/L, and eGFR of 14.

Complete blood count showed hemoglobin of 10.3, platelet of 122, a white cell count (WBC) of 5.02. Electrolytes were normal (Na 143 K 3.69), CO2 was 25.3, Urea was14.5. INR was 1.28. His HBA1c was 6.37%, cholesterol was 2.86, triglycerides was 1.77, LDL was 1.59, HDL was 0.9. Chest X-ray was normal. ECHO revealed an ejection fraction of 60% with no left ventricular hypertrophy and normal diastolic function with a systolic pulmonary artery pressure of 27 mmHg. Urine dipstick showed +1 protein, blood +3. Urine microscopy showed no casts. Urine cell count showed a WBC 0-5, RBC 3-5.

Twenty-four-hour urine protein was 0.44 mgdL. Albumin-Creatinine ratio was 8.131 mg/mmol. He had normal renin and aldosterone ratios. ESR was 42mm/hour. Routine serological tests (Anti-HCV, HBsAg, HIV AB/AG, Varicella-zoster IgG) were normal. No specific antibodies were detected such as anti-neutrophil cytoplasmic antibodies (ANCA), myeloperoxidase or proteinase 3, double-stranded DNA antibodies, anti-cardiolipin IgG and IgM.

Ultrasound (US) renal and bladder revealed bilateral renal gravels; however, no renal masses or hydronephrosis were noted. CT renal without contrast revealed nephropathic renal changes only.

The initial impression was rapidly progressive glomerulonephritis secondary to vasculitis. The patient underwent a renal biopsy and immediately started on a five-day course of 1 gm of IV methylprednisolone.

Renal biopsy revealed 15 glomeruli, 2 of which, were globally sclerosed, see figure 1. Two segmental necrotizing lesions and 1 fibrous crescent were seen. The glomerular basement membranes did not display spikes, splits or holes. About 20% of the cortex is affected by diffuse interstitial scarring; however, only minimal tubular atrophy is seen. The cortical tubules showed severe acute tubular injury and numerous RBC casts. Five small arteries were seen free of lesions. There were no arterial inflammation nor thrombosis.

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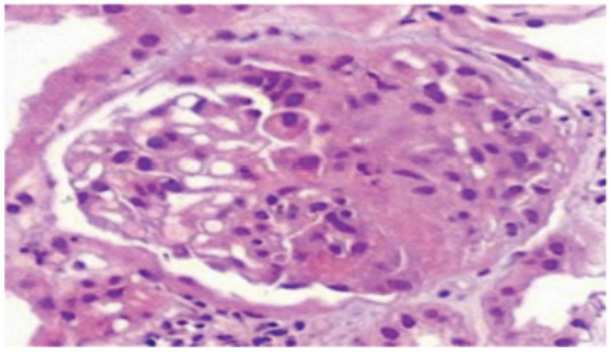

Figure 1: Shows Glomeruli with Scarring Under Light Microscopy, Stained with H&E, PAS, Trichrome and Jones

Renal biopsy under immunofluorescence microscopy revealed that the frozen sections were stained for IgG, IgM, IgA, C3, C1q, kappa and lambda light chains, albumin and fibrinogen, see figure 2. The sample included the cortex and medulla including 5 perfused glomeruli. There were traces of mesangial C3 and IgA.

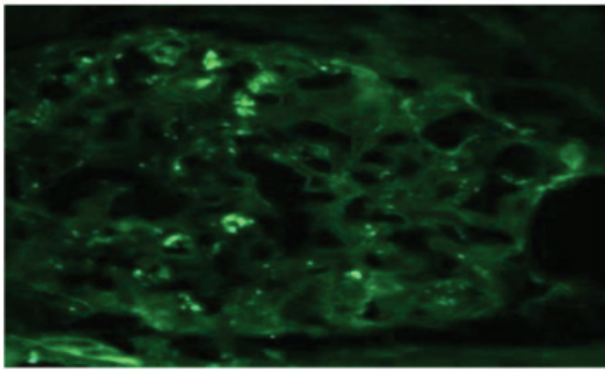

Figure 2: Frozen Sections Seen Under Immunofluorescence Microscopy Showing Traces of Mesangial IgA

Renal biopsy under electron microscopy revealed three glomeruli; the podocytes showed microvillation with cytoplasmic vacuolation. Approximately 25% of the podocyte foot processes were effaced, see figure 3. There was limited segmental widening with the clearing of subendothelial space with occasional electron-dense deposits. Few electron densities were seen in mesangial and paramesangial areas with an increase in the mesangial matrix.

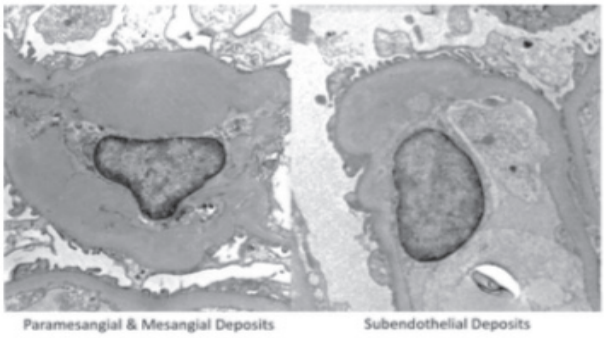

Figure 3: Electron Microscopy Showing Paramesangial and Mesangial Deposits (Left), as Well as Subendothelial Deposits (Right)

The patient was diagnosed with necrotizing crescentic glomerulonephritis, paramesangial and mesangial deposits consistent with IgA nephropathy. Oxford classification score was M1 E1 S1 T0 C0.

The patient received six doses of 500 mg IV cyclophosphamide and slow tapering dose of prednisolone starting at 45 mg once daily orally; for maintenance of immunosuppression tacrolimus 2 gm twice daily orally, which was then increased to 2.5 mg, guided by the level.

The patient had no episodes of hematuria since he was discharged and repeated kidney function tests have shown gradual improvement, the most recent serum creatinine was 126 mmol/L and eGFR 52, see figure 4.

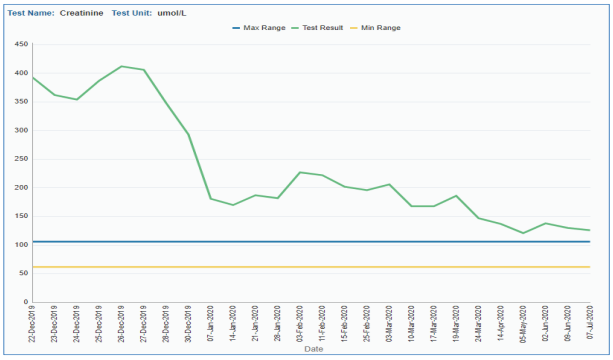

Figure 4: Graph Showing the Decline in the Serum Creatinine after Commencing on Cyclophosphamide and Tacrolimus

DISCUSSION

The KDIGO defines crescentic IgAN as a rapidly progressive deterioration in renal function showing crescents in more than 50% of the glomeruli on a sufficiently obtained renal biopsy[4].

The New Oxford Classification for IgAN uses the MEST-C Score: M=mesangial hypercellularity, S=segmental glomerulosclerosis, T=moderate to severe interstitial fibrosis and tubular atrophy, C=crescents to provide a pathological scoring system for IgAN[4]. The score was updated in 2016 to include crescents after multiple validation studies have found that the presence of any cellular or fibro cellular crescents in patients with IgAN is poor prognostic factors[5-7].

Two risk groups were identified. C1 showed less than 25% crescents which has improved renal outcome with immunosuppression and C2 showed more than 25% crescents and has poor renal function despite immunosuppression[8]. The presence of early to severe cellular crescents in >10% of glomeruli is crescentic IgAN according to some studies[9].

The management of crescentic IgAN has been debated due to the lack of randomized controlled trials[10]. Several studies favored the combined use of corticosteroids and cyclophosphamide[11]. Immunosuppression as a treatment option in IgAN is controversial. In crescentic IgAN, the role of immunosuppression is supported only by subjective data. The poor outcome may be seen with impaired glomerular filtration rate or chronic renal disease[10].

More caution about the use of immunosuppressive regimens is justified in crescentic IgAN. A study showed that 5-year renal survival of patients with crescentic IgAN is 20-40%, irrespective of the therapy[11].

Treatment with immunosuppression in patients with crescentic IgAN have yet to be evaluated in randomized controlled trials, some investigators have argued that RCT is unachievable because of the rarity of crescentic IgAN[10].

In a study, 67% of the 25 patients with diffuse crescentic IgAN treated with immunosuppression showed a stable and adequate kidney function, enough to avoid renal replacement therapy; only 5 required long-term dialysis. A study of 12 patients treated with steroids and intravenous cyclophosphamide revealed favorable outcome[9].

Despite the optimistic observational studies that demonstrate evidence of response to immunosuppression (corticosteroids, cyclophosphamide, and sometimes plasma exchange), there is a significant proportion of patients with crescentic IgAN who do not respond to intensive immunosuppression.

Tacrolimus has been used in organ transplant therapy, there is some evidence in its efficacy in IgAN. However, no evidence is available for the use of tacrolimus specifically in crescentic IgAN; therefore, our use in this patient is controversial.

CONCLUSION

The use of immunosuppression is still controversial. Our case proved that the use of immunosuppression in these patients could improve the clinical outcome and overall quality of life.

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