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## CLINICAL VIGNETTE

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# An IgA Nephropathy with Severe Proteinuria Successfully Controlled with Early Combination Therapy

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### Case

A 51-year-old female presented to Nephrology with acute onset of lower extremity edema and gross hematuria. She reported initial upper respiratory tract infection symptoms followed by significant leg swelling, gross hematuria, and foamy frothy urine. Spot urine showed nearly 13grams of proteinuria, with slightly elevated creatinine from her normal baseline. She had prior chronic microscopic hematuria, with normal kidney function and no proteinuria.

She admitted for urgent kidney biopsy. Pathology revealed IgA nephropathy with diffuse endocapillary and mesangial hypercellularity. Oxford classification was M1, E1, S0, T0, C0, with no significant scarring. She was treated with pulse steroids for 3 days followed by steroid taper. She also received Dapagliflozin, an SGLT2-Inhibitor and Sparsentan, an endothelin and angiotensin 2 receptor antagonist, recently approved for IgA nephropathy.

The patient was tapered off steroids over six months and continued on daily Dapagliflozin and Sparsentan. Her proteinuria continued to improve and her 34-hour urine total protein remained below 500 mg. Her gross hematuria and lower extremity edema resolved and creatinine improved back to her baseline. Blood pressure was also better controlled.

### Discussion

IgA Nephropathy is the most common type of glomerulonephritis worldwide, found more in men and distinctly less in blacks Africans. Presenting symptoms include macroscopic hematuria in 40 to 45% of patients, microscopic hematuria and proteinuria in about 35 to 40% of patients, and nephrotic syndrome or acute renal failure in the remainder. The diagnosis requires finding dominant or codominant mesangial deposition of IgA on immune-histologic biopsy.

While the pathogenesis remains unknown, increasing evidence suggests polyclonal stimulation of immunoglobulins perhaps coupled with structural abnormalities of IgA play pivotal roles. These defects may account for the variety of autoantibodies detected in patients with both IgA Nephropathy and Henoch-Schonlein purpura. While IgA Nephropathy has an indolent course, about 30% of patients will reach ESRD after 20 years,

particularly in those who present with hypertension, heavy proteinuria, or renal insufficiency.

Patients with IgA Nephropathy and little or no proteinuria (<500 mg/day) have low risk of short-term progression. Those with > 3mgs/day proteinuria have 25-fold faster decline in renal function.<sup>1,2</sup>

Treatment of IgA Nephropathy has been challenging and mostly involve steroids, which have significant side effects. For that reason, steroids are not able to be used long term.

The recent clinical trial PROTECT showed Sparsentan, a novel, non-immunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist, significantly reduced proteinuria versus irbesartan, an angiotensin II receptor blocker, for treatment of IgA Nephropathy. Over 110 weeks, treatment with once daily Sparsentan versus maximally titrated irbesartan in patients with IgA Nephropathy resulted in significant reductions in proteinuria and preservation of kidney function. Safety of Sparsentan was similar to irbesartan.<sup>3,4</sup>

### Conclusion

Treatment of IgA nephropathy remains challenging despite being first described in 1968 by Jean Berger. To date, most treatments have been based on immune-suppressive medications, which may have serious side effects. Recently, Sparsentan, a non-immunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist agent, has given new hopes for IgA Nephropathy treatment. Our patient shows the importance of early detection and treatment of IgA nephropathy. This patient also shows benefit of combination therapy including use of dual endothelin angiotensin receptor antagonist agent along with SGLT 2 inhibitor to successfully reduce severe proteinuria to an acceptable range of below 500 mg. Proteinuria remains a prognostic factor in IgA nephropathy.

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