Title

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CLINICAL VIGNETTE

Induction of Near Complete Remission of Steroid Dependent Tip Variant-Focal and Segmental Glomerulosclerosis with Addition of a Calcineurin Inhibitor

Glucocorticoids May Not Be Enough Even for the Most Steroid Sensitive Variant

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Introduction

Focal and Segmental Glomeruloscerlosis (FSGS) is a pattern of renal injury usually resulting in nephrotic range proteinuria.[1] The etiology maybe primary due to an autoimmune process,[1] though the actual pathogenic molecule or antibody is debated.[2] Soluble urokinase Plasminogen Activator Receptor (SuPAR) was thought to be the circulating permeability factor hypothesized to cause primary FSGS.[2] Secondary FSGS can be caused by a myriad of conditions including Human Immunodeficiency Virus (HIV), other viruses, obesity, diabetes, hypertension, chronic nephron loss from other glomerular diseases, solitary kidney,[3] certain medications (such as bisphosphonates and Vascular Endothelial Growth Factor [VEGF] and tyrosine kinase inhibitors [TKI]).[4]

There are four variants of FSGS[5] listed in order of decreasing steroid sensitivity 1. Tips variant 2,3. Perihilar and cellular 4. Collapsing FSGS. The "Not Otherwise Specified," (NOS) variant: does not fit into the above classification scheme.[5] The Tips variant tends to be steroid sensitive and the collapsing variant tends to be treatment refractory.[5] The collapsing variant is often seen as HIV associated nephropathy (HIVAN) in African American patients with uncontrolled HIV virus replication.[6,7] Recent genetic advances have identified certain ApoL-1 variants as contributing to a genetic susceptibility to nephrosclerosis and hypertension later in life,[8] besides the known childhood steroid resistant nephrotic syndrome gene mutations in nephrin and podocin.[9]

We report a 54-year-old female who developed massive proteinuria due to Tips variant FSGS. She was initially treated with steroids with a dramatic response that plateaued. High dose steroid metabolic side effects necessitated tapering, which led to a relapse. The addition of calcineurin inhibitors (cyclosporine) led to a stabilizing of proteinuria and allowed rapid tapering of steroids to safer levels.

Case Report

A 54-year-old female first presented with severe lower extremity swelling, fatigue, and proteinuria, with a urine protein to creatinine ratio of 29 grams protein/gram creatinine. Her 24-hour urine protein matched this at 30 grams protein/24 hour period. Extensive rheumatological testing failed to identify any autoimmune serologies, with negative ANA, anti dS DNA, RPR. The patient was also hypertensive, and had chronic kidney disease stage IIIa with estimated glomerular filtration rate of 49-55, though serum creatinine was 0.92 mg/dL. The serum creatinine increased to 1.4 mg/dL from acute kidney injury due to the massive proteinuria. She did not use non-steroidal anti-inflammatory drugs or had exposure to other nephrotoxins. Renin-Angiotensin-Aldosterone (RAAS) blockade was initiated as a first step to control proteinuria. Figure 1 graphs serum creatinine, urine protein, from presentation through treatment course.

Renal biopsy was performed and showed Tip variant FSGS with 5% global and 45% segmental glomeruloscerlosis. On the light microscopy eight glomeruli were noted with 1 globally sclerosed and 3 with segmental sclerosis. Moderate tubulo-intersitital inflammation was noted in the tubules, and the primary areas with sclerosis were the glomerular tips. Immunoflouresnce was negative. Electron microscopy showed 90% podocytes foot process effacement, which is a feature typical of minimal change (nil-disease), and FSGS. Importantly the appearance of the lesion was more typical of primary FSGS than secondary FSGS, which was in differential diagnosis due to a body weight of 100kg. Figure 2 shows her biopsy which demonstrates Tip variant FSGS.

She was started on high dose steroids (1mg/kg) of ideal body weight, (about 60 kg) for a planned treatment of 2 ½ -3 months before slowly tapering over 3 more months to a dose of 5-10 mg prednisone/week depending on the treatment response. Cotrimoxazole for pneumocystis prophylaxis, calcium carbonate/vitamin D, and histamine two receptor blockers (H2) were given along with the high dose steroid therapy.

She had an initial drop in urine protein from 29 grams to a urine protein / creatinine ratio of 3.8 grams protein/gram creatinine and achieved a nadir of 1.9 grams protein/ gram creatinine two and half months after starting the therapy before tapering was initiated. She noted weight gain, edema, skin changes, and

worsening hypertension on glucocorticoids. When steroids had been tapered slowly from 60 mg to 45 mg, her urine protein increased back to 5.5-6.3 grams, four months after start of therapy. She was increased back to 60 mg of steroids again but experienced worsened side effects.

At this point nearly 4 months after starting steroids, Cyclosporine was started to supplement steroids at a dose of 100-150mg of cyclosporine twice a day for a goal trough of 75-150 ng/ml [optimal goal towards 100 ng/ml]. Urine protein decreased further to 3-4 gram protein/gram creatinine range and stabilized. After starting cyclosporine, the prednisone was successfully tapered from 60 mg to 15mg daily. This resulted in improvements in blood pressure, weight, metabolic profile, energy, mood, and wellbeing. The latest 24 hour urine protein measurement indicated a near complete remission with urine protein to 0.7 grams/day. Refer to Figure 1 for the graphical trends showing drop in urine protein with addition of steroids, and the further improvement allowing tapering of steroid dose and induction of a more complete remission.

Discussion

The clinical treatment of FSGS is immunosuppression,[10] and the current evidence suggests that there are safer alternatives alkylating agents which have been used historically. Steroids are the first line treatment, though steroid treatment failure or dependence often occurs.[10] The Tips variant tends to be the most steroid responsive as stated before, in cases where steroid treatment failure or dependence occurs calcineurin inhibitors are useful as an adjunct or steroid sparing agent.[10] This approach often allows steroids to be tapered and the disease to be brought into some level of control.[10] There are other agents available like Adrenocorticotropic Hormone (ACTH) gel but the evidence supporting its use is more limited to a few small case series reported.[11] No immunosuppression is indicated for secondary FSGS, with the only intervention being treating the underlying cause of renal disease-if possible.[12]

The core message is that steroid treatment of even steroid sensitive variants of primary FSGS can fail or produce an incomplete result with nephrotic levels of proteinuria. Calcineurin inhibitors is an effective adjunctive agent to allow for disease control while limiting the metabolic side effects of glucocorticoids.

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Figures

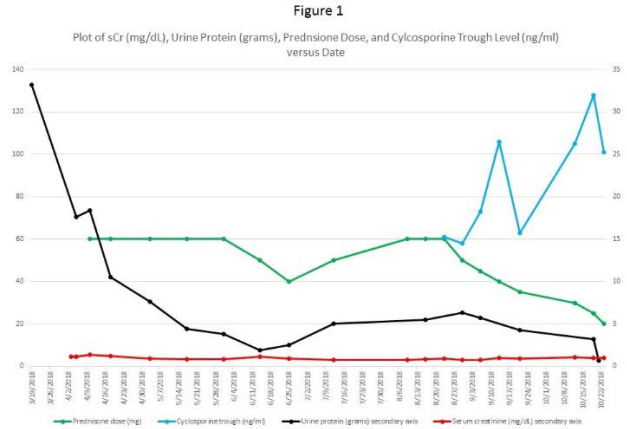

Figure 1: Graph of serum creatinine (mg/dL), urine protein (grams protein), steroid dose (mg), and cyclosporine trough (ng/ml) versus time showing initial response of disease to steroids and a more complete remission with addition of calcineurin inhibitors.

Figure 2

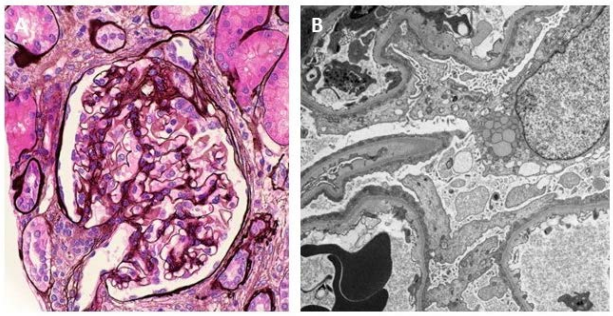

Figure 2: Renal biopsy slides demonstrating Tip variant FSGS
A) Light microscopy 40x Hematoxylin and Eosin demonstrating focal and segmental glomeruloscerlosis at tip of glomerulus consistent with Tip variant FSGS.
B) Electron micrograph demonstrating 90% podocytes effacement that can be consistent with FSGS.

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