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Combined Therapy of Cyclosporine A, Mycophenolate, Losartan, and Finerenone in Drug-Resistant NOS-Focal Segmental Glomerulosclerosis

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Abstract

Background: Focal and segmental glomerulosclerosis (FSGS) is a common and progressive podopathic glomerulopathy that is resistant to treatment with corticosteroids (70%) and calcineurin-inhibitors (50%). Hence, its primary phenotype is associated with kidney loss in 50% of those with persistent nephrotic syndrome (NS) within 3 - 8 years of diagnosis. The Case: A 26-year-old woman presented with severe NS, hypertension, and hematuria. Investigations excluded genetic mutations, chronic drug use, kidney maladaptations, autoimmune disorders, chronic infections, and toxin exposure. Her kidney biopsy showed focal and segmental glomerular sclerosis with synechial adhesion without cellular proliferation and necrosis, or basement membrane thickening and collapse. On electron microscopy, it showed diffuse effacement of podocyte foot processes. Hence, she had non-otherwise specific FSGS. Her hypertension was controlled with losartan, yet her severe NS (proteinuria > 9 g/day and hypoalbuminemia < 16 g/L) persisted despite sequential 3 months of corticosteroids 60 mg daily, followed by another 3 months of cyclosporine A (CsA) at 100 mg twice daily. However, she responded after the addition of mycophenolate mofetil (MMF) to CsA. Since she was resistant to CsA before, a trial to discontinue it 6 months later was followed by relapse of NS. Hence, CsA was reinstituted, and she responded to it again. At that time, rituximab could not be used due to infusional allergic reactions. After 1 year, the dose of CsA was reduced to 50 mg twice daily to avoid long-term CsA-interstitial fibrosis. Moreover, she remained on losartan and finerenone to decrease glomerular hyperfiltration. By 2 years of follow-up, she remained well with minimal pro-

teinuria (400 mg/day) and normal creatinine clearance (1.8 ml/second). Conclusion: In primary FSGS, multiple mediators may be acting simultaneously and require combined immunosuppressants.

Keywords

Calcineurin Inhibitors, Corticosteroid Resistant, Cyclosporine A, Focal Segmental Glomerulosclerosis, Mycophenolate Mofetil, Nephrotic Syndrome

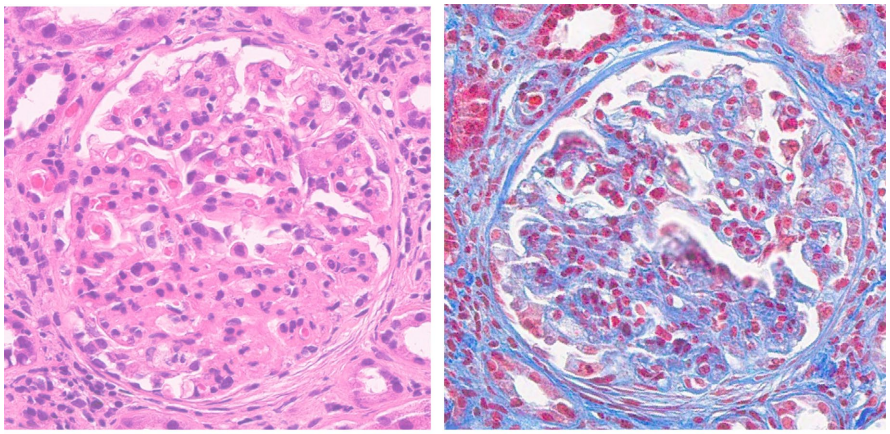
1. Introduction

Focal segmental glomerulosclerosis (FSGS) is a histopathological disorder that starts with focal (not diffuse) and segmental (not global) glomerular scarring [1]. It is a podopathy, *i.e.*, a disease of the glomerular podocytes with effacement of foot processes of visceral epithelial cells and hence progressive proteinuria up to nephrotic syndrome (NS). It accounts for 40% of nephrotic syndrome cases in adults and 20% in children [2]. Its annual incidence is between 0.2 to 1.8 per 100,000 population with male and black predominance [2]. It can result from an idiopathic (primary) disorder, genetic mutations (APOL1, NPHS1 and NHPS2), secondary autoimmune diseases, hypertension, infections, drugs, toxins, and hemodynamic maladaptations due to congenital anomalies, previous trauma, surgery, obesity, sickle cell anemia, transplanted kidney, or maltreated kidney diseases [3]. NS is the most common presentation (70%), which is usually associated with hematuria, hypertension, and progressive renal loss. Hence, histopathological diagnosis and accurate identification of the underlying etiology are crucial for guiding treatment decisions, predicting prognosis, and assessing transplant risks [4]. Management of its secondary causes, with means to decrease glomerular hyperfiltration with ACEI and ARB, is essential to limit its progression if started early. On the other hand, 70% of primary FSGS is corticosteroid resistant, and the genetic (familial) one is resistant to immunotherapy [1] [5]. Approximately 50% of patients with persistent nephrotic-range proteinuria progress to ESRD within 3 to 8 years of an FSGS diagnosis [6]. In this case presentation, we present a patient with multi-drug resistant FSGS that responded to combination immunosuppressive therapy, indicating a multi-channel etiology for this phenotypic disease presentation.

2. The Case

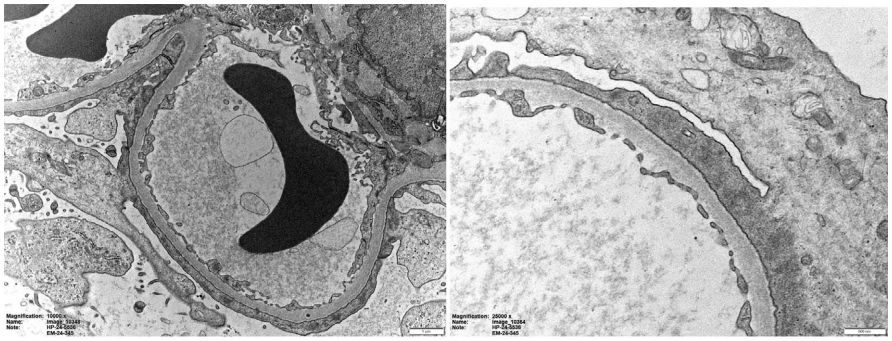
A 26-year-old woman was referred to our center with a history of progressive lower limb oedema for 4 months. She did not have a past history of previous medical disease, surgeries, allergies, or chronic intake of drugs. Moreover, she did not have a family history of primary nephrotic syndrome. On her initial physical examination, she was conscious and oriented. She was afebrile and had a body weight of 106 kg. Blood pressure was 160/110 mmHg. She had buffy eyelids, 3(+)

lower limbs and sacral edema, yet without jugular venous distension and lymphadenopathy. Systemic examination did not show abnormality. Her initial laboratory investigations showed normal peripheral leukocytic and platelet counts. Hemoglobin was 110 g/L with normal MCV. Serum glucose, urea, creatinine, electrolytes, and liver functions were normal except for albumin at 16 g/L. Serum cholesterol was 8 mmol/L. TSH was normal. Urine routine and microscopy showed 4(+) proteinuria and hematuria, yet without pyuria. Serum complements (C3 & C4), IgA, and protein electrophoresis were normal. ANA, anti-ds DNA, ANCA, anti-GBM antibodies, RA, hepatitis B surface antigen, and anti-HCV antibodies were negative. Genetic tests did not show mutations. Procalcitonin level was normal and blood cultures did not disclose infection. HIV testing was negative. Twenty-four-hour urine showed creatinine clearance at 1.6 ml/second and protein excretion at 9 mg/day. Chest x-ray was normal. Abdominal and pelvic ultrasound revealed normal-sized kidneys, yet with increased cortical echogenicity and moderate ascites. Initially, she required combinations of Albumin-Furosemide infusions to control her symptomatic edema, followed by a daily combination of Furosemide 80 mg and Fineronone 10 mg. Blood pressure was controlled with Losartan 100 mg daily. Percutaneous kidney biopsy showed a total of 20 glomeruli. On H&E and trichrome examination, all appeared normal except for 1 that showed segmental sclerosis with synechial adhesion without cellular proliferation and necrosis or basement membrane thickening and collapse (**Figure 1(a)** & **Figure 1(b)**). Electron microscopy revealed diffuse effacement of podocyte foot processes (**Figure 2(a)** & **Figure 2(b)**). As seen in **Table 1**, she did not respond to Prednisone 1 mg/kg for 6 weeks. Hence, Cyclosporine A (CsA) 100 mg twice daily was added. Despite adequate blood levels of the drug, her serum albumin remained at 16 g/L and she remained dependent on frequent Albumin-Furosemide infusions to control her edema. Hence, Mycophenolate mofetil (MMF) was added at a dose of 1 g twice daily. With such a drug combination, she showed



(a) (b)

Figure 1. Photomicrograph of a kidney biopsy showing a glomerulus with segmental sclerosis and synechial adhesion to the Bowman capsule, stained with H&E ×40 (a) and Masson's trichrome ×40 (b).



(a) (b)

Figure 2. Photomicrograph of an electron microscopic view of a kidney biopsy showing diffuse effacement of podocyte foot processes, magnified ×10,000 (a) and 25,000 (b).

Table 1. Clinical and biochemical changes, over time, of a patient with NOS-FSGS treated with combined immunosuppressive drugs.

Time (months)		−6	−3	0	2	4	6	7	9	12	24
Age, gender & race: 26 years, female, White											
Clinical Data											
Presentation:	Generalized edema × 4 months	2(+)	2(+)	3(+)	3(+)	(−)	(−)	(+)	(−)	(−)	(−)
	Blood pressure (120 - 80 mmHg)	160/110	120/80	120/80	120/80	120/80	120/80	120/80	120/80	120/80	120/80
	Body weight (Kg)	98	100	106	106	100	98	101	96	94	95
Laboratory tests*											
Serum	Albumin (35 - 50/L)	21	18	16	19	33	36	26	32	36	37
	Creatinine (60 - 120 μmol/L)	82	96	102	101	98	84	90	89	82	81
	LDL-Cholesterol (<3 mmol/L)	6	8	10	9	7	4	5	4	3	3
24-hour urine for	Creatinine clearance (1.7 - 2.3 ml/second)	1.7		1.6		1.8		1.7	1.8	1.7	1.8
	Protein output (g/day)	4	6	9	4	2	1	5	1	0.6	0.4
Drug therapy*											
	Prednisone: 80 mg X1										
	Cyclosporine A		100 mg X1					100 mg X1		50 mg X1	
	Mycophenolate mofetil: 1 g × 2										
	Losartan: 100 mg X1										
	Fineremone: 10 mg X1										
	Furosamide	40 mg	40 mg X1				40 mg X1				

*Daily dose; X1: once daily, X2: twice daily.

gradual improvement over the next 4 months with clearance of edema, lack of Furosemide need, increase of serum albumin to 33 g/L, and decreased protein output to 2 g/day with normal creatinine clearance. Since she was resistant to CsA before, a trial to discontinue it 6 months later was followed by relapse of NS. Hence, CsA was reinstituted and she responded to it again. At that time, Rituximab could not be used due to infusional allergic reactions. Hence, she was kept on the same combination till 12 months. Subsequently, the dose of CsA was reduced safely to a maintenance dose of 50 mg twice daily. By 24 months, she remained clinically stable and with near-normal biochemistry. With CsA, significant medication side effects were encountered, viz. hypertension, hirsutism, skin darkening, and gum hyperplasia. Moreover, no significant ones were observed with MMF, viz. abdominal pains, diarrhea, and infections.

3. Discussion

The pathogenesis of FSGS involves a complex interplay among several cell types, including podocytes, endothelial cells, and the basement membrane. Foot process effacement, along with the proliferation of mesangial, endothelial, and epithelial cells, occurs early in the disease course. This is followed by the collapse or shrinkage of glomerular capillaries, ultimately leading to scarring (glomerulosclerosis) [7]. In the primary form of FSGS, multiple soluble permeability factors may mediate these structural changes, including corticotrophin-like cytokine factor 1, apoA1-b, anti-CD40 antibodies, and suPAR [8]. Histologically, FSGS is classified into five variants: perihilar, tip, cellular, collapsing, and not otherwise specified (NOS), with significant differences in baseline clinical characteristics, better outcomes in tip and perihilar, and worse in the rest of the variants [9]. Our patient had NOS-FSGS, with its synechial adhesions and diffuse effacement of podocyte foot processes indicating a primary etiology [3]. Lack of IgM and C3 deposition is expected, with limited sclerotic glomeruli in the sampled sections [10]. In corticosteroid-resistant FSGS, various immunosuppressive drugs have been explored, viz. Sparsentan, MMF, Rituximab, Cyclophosphamide, mTOR inhibitors, Azathioprine, Levamisole, Mizorbine, Adalimumab, Pirfenidone, Fresolimumab, Saquinavir, Abatacept, and Adrenocorticotropic hormone gel. Unfortunately, all had limited efficacy when used alone [3]. Our patient did not respond to sequential immunosuppressive therapy, with corticosteroids followed by CsA. Hence, we elected to use a combination of MMF and CsA, and such a combination showed an adequate response. CsA inhibits T-helper cells without affecting phagocytosis, while MMF acts by inhibiting T- and B-cell activation and proliferation [11] [12]. A trial to remove CsA and continue only with MMF was followed by relapse, indicating that remission in our patient was not due to MMF alone, but to the drug combination. Fortunately, she responded after reinstitution of CsA. In our patient, her gradual response indicated that multiple mediators may be operating, even in an individual patient with NOS-FSGS. Such combined immunosuppressive therapy was used by us before in refractory idiopathic glomerulopathy, and

hence we elected to use it in our current patient [13]. The choice of MMF instead of Cyclophosphamide was to avoid its long-term gonadotoxic impact [14]. A similar study has shown that combination of adrenocorticotropic hormone gel with Tacrolimus (a calcineurin inhibitor) was more effective than individual agents in FSGS [3]. After 12 months of our combination therapy, we tried to reduce the CsA dose to just 50 mg ×2 to avoid its long-term side effects, especially interstitial fibrosis [15]. Fortunately, it remained efficacious despite the lower therapeutic level, yet safe long-term. Such a combination was used since other, safer, and more practical protocols using Rituximab could not be implemented due to severe immediate infusional reactions [16].

4. Conclusion

In primary FSGS, multiple mediators may be acting simultaneously and require combined immunosuppressants.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon request.

Written informed consent for publication of the case is available upon request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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