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【 CASE REPORT 】

Successful Treatment of Nephrotic Syndrome Due to Collapsing Focal Segmental Glomerulosclerosis Accompanied by Acute Interstitial Nephritis

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Abstract:
A 39-year-old woman was hospitalized for nephrotic syndrome. Laboratory test results showed increased serum creatinine levels and urinary excretions of beta-2-microglobulin, and N-acetyl-beta-D-glucosaminidase. A renal biopsy revealed collapsing focal segmental glomerulosclerosis (FSGS) and acute interstitial nephritis. Despite treatment with pulse steroid followed by oral high-dose glucocorticoids and cyclosporines, heavy proteinuria persisted. After low-density lipoprotein apheresis (LDL-A) therapy was initiated, her proteinuria gradually decreased, leading to complete remission. A repeat renal biopsy after treatment revealed no collapsing glomeruli. Immediate LDL-A should be performed to treat cases of collapsing FSGS poorly responding to other treatments.

Key words: nephrotic syndrome, collapsing focal segmental glomerulosclerosis, steroid, cyclosporin, low-density lipoprotein apheresis

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Introduction

Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome and can be classified into five pathological variants (1). Among its variants, collapsing FSGS comprises approximately 12% of all cases. It has the lowest remission rate (13.2%) and the highest incidence rate of end-stage renal disease (65.3%) (2). Collapsing FSGS is characterized by global or segmental collapse of the glomerular capillary tuft with overlying visceral epithelial cells showing hypertrophy and hyperplasia (1, 2). To date, there has been no evidence-based treatment of collapsing FSGS (3).

We herein report a rare case of nephrotic syndrome due to collapsing FSGS. This case was successfully treated with a combination of steroids, cyclosporine, and low-density lipoprotein apheresis (LDL-A), resulting in complete remission. Biopsy specimens after treatment revealed no collapsing glomeruli.

Case Report

A 39-year-old woman was admitted to our hospital for anasarca and dyspnea. She had no significant medical history or allergies. She received no medications. Her baseline serum creatinine (sCr) levels and urine test results were unknown. On admission, her vital signs were as follows: blood pressure, 117/91 mmHg; temperature, 36.9°C; pulse, 96/min; and respiratory rate, 16/min. She presented with extensive pitting peripheral edema.

The laboratory findings are summarized in Table. A urinalysis revealed proteinuria (15.9 g/gCr) and hematuria (sediment red blood cells, 20-30 per high-power field). Uri-

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Table. Laboratory Data.

Blood					
WBC	7,400 /μL	Triglyceride	216 mg/dL	Anti-centromere Ab	–
RBC	3.85×10^6 /μL	LDL-cholesterol	471 mg/dL	PT-INR	1.00
Hemoglobin	11.5 g/dL	HDL-cholesterol	74 mg/dL	APTT	38.1 sec
Hematocrit	33.2 %	C-reactive protein	0.16 mg/dL	LA	–
Platelet count	299×10^3 /μL	ASO	<10 IU/mL	aCL IgG	<2
Total protein	4.5 g/dL	IgG	319 mg/dL	Anti-CL β_2GP1 ab	–
Albumin	1.4 g/dL	IgA	120 mg/dL	HBs Ag	–
Total bilirubin	0.4 mg/dL	IgM	132 mg/dL	HCV Ab	–
BUN	82.8 mg/dL	IgE	261 IU/mL	HIV Ab	–
Creatinine	8.72 mg/dL	C3	122 mg/dL	T-SPOT	–
Uric acid	7.3 mg/dL	C4	50.7 mg/dL	Iron	58 μg/dL
AST	31 mg/dL	CH50	53 mg/dL	TIBC	292 μg/dL
ALT	22 IU/L	ANA	<40	Ferritin	62.0 ng/mL
LDH	301 IU/L	Anti-ds DNA ab	–	Folate	1.7 ng/mL
ALP	181 IU/L	MPO-ANCA	–	Vitamin B12	284 pg/mL
γGTP	20 IU/L	RP3-ANCA	–		
CK	274 IU/L	Anti-GBM Ab	–	Urine	
Sodium	130 mEq/L	Cryogloblin	–	Dipstick protein	3+
Potassium	3.0 mEq/L	Anti-Sm Ab	–	Occult blood	3+
Chloride	100 mEq/L	Anti-SS-A Ab	–	RBC	20-30 /HPF
Calcium	7.2 mg/dL	Anti-SS-B Ab	–	Protein	15.9 g/gCr
Phosphorus	7.2 mg/dL	Anti-U1-RNP Ab	–	β_2 MG	3920 μg/gCr
FPG	106 mg/dL	Anti-Scl-70 Ab	–	NAG	109.5 U/gCr
HbA1c	6.0 %	Anti-Jo-1 Ab	–		

WBC: white blood cell, RBC: red blood cell, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ Γ T Π : γ-glutamyl transpeptidase, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, LDL: low density lipoprotein, Ig: immunoglobulin, C3: complement component 3, C4: complement component 4, CH50: 50% hemolytic complement, ANA: antinuclear antibody, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase-3 anti-neutrophil cytoplasmic antibody, GBM: glomerular basement membrane, Sm: Smith, RNP ribonucleoprotein, Scl: scleroderma, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, LA: lupus anticoagulant, aCL: anticardiolipin antibodies, CL β_2GP1: cardiolipin $\beta_2$glycoprotein I, HBs: Hepatitis B surface, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, TIBC: Total iron binding capacity, HPF: high power field, β_2 MG: beta2-microglobulin, NAG: N-acetyl-beta-D-glucosaminidase

nary excretions of beta2-microglobulin (MG) and N-acetyl-beta-D-glucosaminidase (NAG) were markedly elevated (3,920 μg/gCr and 109.5 U/gCr, respectively). Her blood urea nitrogen and sCr levels were elevated at 82.8 mg/dL and 8.72 mg/dL, respectively. She had low serum total protein and albumin levels at 4.5 g/dL and 1.4 g/dL, respectively. Her low-density lipoprotein cholesterol level was 471 mg/dL. Based on these results, she was diagnosed with nephrotic syndrome.

Serological testing revealed normal levels of complement-fixing antibody and anti-streptolysin O (ASO). She also tested negative for anti-nuclear, anti-double strand DNA, anti-Sm antibodies. In addition, she tested negative for anti-Sjögren's syndrome A, anti-Sjögren's syndrome B, anti-U1 ribonucleoprotein, anti-scleroderma-70, anti-Jo-1, anti-centromere, anti-glomerular basement membrane, myeloperoxidase anti-neutrophil cytoplasmic, and proteinase 3 anti-neutrophil cytoplasmic antibodies. Furthermore, she tested negative for β_2 glycoprotein-1 (β_2GP-1), lupus anticoagulant, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus (HIV). Urine and serum protein electrophoresis revealed no monoclonal spikes. Chest and abdominal computed tomography revealed ascites and bilateral kidney swelling without atrophic changes. Renal ultrasound showed swollen kidneys (right, 11.2×5.1 cm; left, 11.3×6.4 cm) without dilation of the urinary tract, renal pelvis, or calyces. The corticomedullary junction was obscured from view. The renal arterial resistive index was normal (right: 0.61; left: 0.61).

After admission, hemodialysis was initiated due to oliguria. We performed a renal biopsy. There were 19 glomeruli, 1 of which was globally sclerotic. Several glomeruli revealed collapse of the glomerular capillary tufts, podocyte hypertrophy (Fig. 1a), and segmental sclerotic lesions (Fig. 1b). Several glomeruli were normal (Fig. 1c). Diffuse interstitial nephritis independent of glomerular damage was identified (Fig. 1d). Interstitial fibrosis and tubular atrophy were found. Immunofluorescence staining for mesangial areas and focal segmental glomerulosclerosis revealed focal and segmental deposition of IgG, IgM, C3

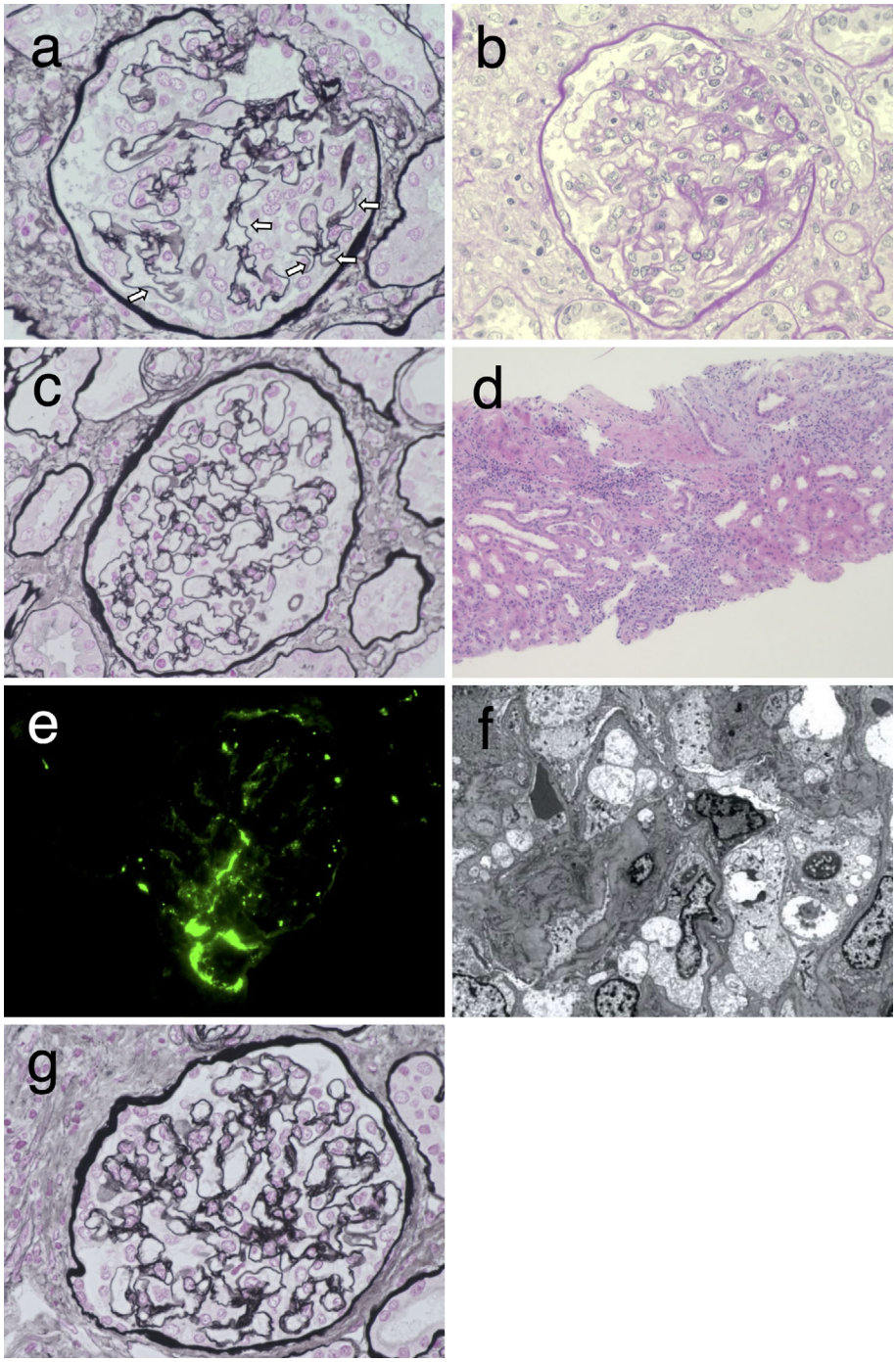

Figure 1. **Renal biopsy specimen on light microscopy. (a) Collapse of the glomerular capillary tufts, and podocyte hypertrophy. Periodic acid-methenamine silver staining (400× magnification); (b) Segmental sclerosis. Periodic acid-Schiff staining (400× magnification); (c) Normal glomeruli. Periodic acid-methenamine silver staining (400× magnification); (d) Diffuse interstitial nephritis. Hematoxylin and Eosin staining (100× magnification); (e) Immunofluorescence staining shows global glomerular tuft staining for C3 (400× magnification); (f) Electron microscopy shows podocyte foot process effacement and mesangial sclerosis with increased matrix (1,500× magnification); (g) Non-collapse of the glomerular capillary tufts after treatment. Periodic acid-methenamine silver staining (400× magnification).**

(Fig. 1e), fibrinogen, kappa light chains, and lambda light chains. Electron microscopy showed diffuse foot process effacement and mesangial sclerosis with increased matrix. Furthermore, there were no immune complex deposits (Fig. 1f). Based on these findings, a diagnosis of collapsing FSGS and acute interstitial nephritis (AIN) was established.

The clinical course of the patient is shown in Fig. 2. After confirming this diagnosis, she was treated with steroids, including methylprednisolone pulse therapy. However, this treatment did not sufficiently decrease her proteinuria.

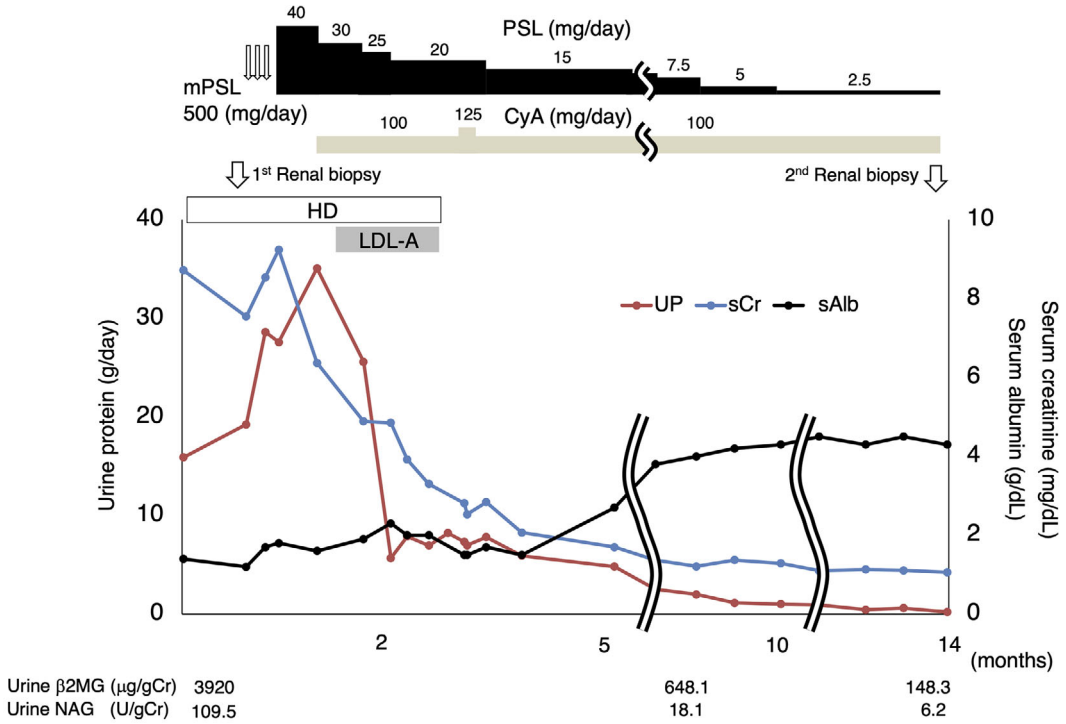

Figure 2. **The clinical course of the patient. LDL-A: low-density lipoprotein apheresis, HD: hemodialysis, UP: urine protein, sCr: serum creatinine, sAlb: serum albumin, MG: microglobulin, NAG: N-acetyl-beta-D-glucosaminidase, PSL: prednisolone, mPSL: methylprednisolone, CyA: cyclosporine**

Therefore, cyclosporine was added concomitantly. Blood cyclosporine levels were maintained within 600-800 ng/mL for 2 hours after oral administration. Due to an insufficient response, LDL-A therapy was initiated (Liposorba LA15; Kaneka, Osaka, Japan). Approximately 4,000-5,300 mL of plasma was administered per session. During the 12 LDL-A sessions, her proteinuria gradually decreased, while the serum albumin levels and urine output increased. Complete remission was achieved 14 months after initiation of treatment. Her β2-MG-uria and NAG-uria also gradually improved to 148.3 μg/gCr and 6.2 U/gCr, respectively, during the 14-month follow-up (Fig. 2). A repeat biopsy revealed 48 glomeruli, 3 of which were globally sclerotic. However, there were no glomeruli with collapse (Fig. 1g). She remained in complete remission with cyclosporine administration alone.

Discussion

We herein report a 39-year-old woman without HIV infection who presented with nephrotic syndrome and acute kidney injury due to idiopathic collapsing FSGS. Collapsing FSGS is frequently observed in patients with HIV. Secondary FSGS was associated with various etiologies, including infections, autoimmune disorders, drugs intake, and malignancies (4). In the present case, other causes were not identified. Therefore, the patient was diagnosed with idiopathic collapsing FSGS. The precise pathogenesis and etiology of idiopathic collapsing FSGS remain unclear (5).

This patient developed nephrotic-range proteinuria at the onset. However, her serum creatinine level at the onset was higher than that of previously reported cases (4.2 mg/dL) (6). Collapsing FSGS generally responds poorly to steroids or immunosuppressive agents (2). In this case, since urinary protein excretion persisted after treatment with steroids and cyclosporin, LDL-A was initiated. LDL-A can be effective in drug-resistant nephrotic syndrome, particularly FSGS. It lowers lipid levels and improves the bioavailability of steroids and calcineurin inhibitors (7). Development of collapsing FSGS is affected by various unknown factors absorbed by dextran sulfate cellulose filters. Previous studies have reported collapsing FSGS cases treated with LDL-A (8, 9). In one case, complete remission was achieved. However, nephrotic syndrome relapsed (8). In another case, the disease was progressive, and remission was not achieved (9). LDL-A should be immediately performed when patients with drug-resistant nephrotic syndrome do not respond to primary medications (7). In our case, we applied LDL-A earlier with a combination of steroids and cyclosporine, which might have significantly contributed to improving initial treatment responsiveness. Collapsing FSGS is a pathological feature of severe glomerular injury, related to glomerular ischemia (10). Although the FSGS lesion was focal, and glomeruli sampled in the first and repeat biopsy were different, the collapsing FSGS improved. These changes may attenuate nephrotic syndrome and normalize serum creatinine levels.

Some factors contribute to collapsing FSGS complicated

by AIN, such as HIV, malaria, and bisphosphonate (11-13). In the present case, however, these factors were unlikely, and diffuse interstitial nephritis independent of glomerular damage was identified. Therefore, we considered the patient's AIN to have developed independently from collapsing FSGS. AIN has multiple etiologies, including drug-induced, infectious, systemic, autoimmune, genetic, and idiopathic ones. However, the precise causative factors of AIN in this case were uncertain. The improvement of β2-MG-uria and NAG-uria also suggests that the attenuation of AIN might have induced improvements in the renal function.

In conclusion, we encountered a rare case of a patient with attenuation of collapsing glomeruli after immediate treatment with LDL-A. This treatment of collapsing FSGS may be a potential treatment for patients poorly responding to other treatments.

The authors state that they have no Conflict of Interest (COI).

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