Focal Segmental Glomerular Sclerosis Ameliorated by Long-term Hemodialysis Therapy with Low-density Lipoprotein Apheresis

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Abstract

We report a case involving a 43-year-old Japanese woman with steroid-resistant focal segmental glomerular sclerosis (FSGS) and severe renal dysfunction, which was ameliorated by low-density lipoprotein apheresis (LDL-A). She had been treated with steroid therapy, but had experienced anuria for over 10 weeks and required hemodialysis. She was then treated with LDL-A, which resulted in improved urinary protein excretion and renal function. Her renal function recovered after 97 days of hemodialysis therapy. This case suggests that LDL-A may represent an effective rescue treatment in patients with FSGS and long-term anuria.

Key words: focal segmental glomerular sclerosis, LDL apheresis, hemodialysis, acute kidney injury, nephrotic syndrome

(Intern Med 54: 2213-2217, 2015)
(DOI: 10.2169/internalmedicine.54.4631)

Introduction

Focal segmental glomerular sclerosis (FSGS) is one of the most common causes of primary glomerular disease (1). FSGS is present in 10-15% of patients undergoing an evaluation for proteinuria (2). Minimal change disease (MCD) is also one of the most common causes of primary glomerular disease (3, 4), and it is difficult to distinguish between MCD and FSGS in a single renal biopsy. In a previous report of 49 MCD patients with repeat biopsies, 14 were diagnosed with FSGS (5). In a Japanese report, the rates of MCD and FSGS in patients with nephrotic syndrome (NS) were 33.2% and 6.1%, respectively (6).

Acute kidney injury (AKI) is a common complication of FSGS (7). It has been reported that a small proportion of severe AKI patients require hemodialysis (8, 9). However, recovery after long-term end-stage renal dysfunction is rare.

Low-density lipoprotein apheresis (LDL-A) has been used in the treatment of drug-resistant NS, especially FSGS, but there are no reports of its use in patients with long-term end-stage renal disease.

We herein report a case of drug-resistant NS, resulting from FSGS complicated by severe AKI, which required long-term hemodialysis therapy. The patient recovered following LDL-A therapy.

Case Report

A 43-year-old Japanese woman was referred to our hospital due to nausea and lower limb edema. She weighed about 7 kg more than normal 8 days after onset. An examination revealed the following: height 150.0 cm, weight 40.0 kg, body temperature 36.8°C, blood pressure 129/75 mmHg and a regular heart rate of 64 beats/min. Auscultation revealed normal heart and respiratory sounds, and a neurological examination was normal. Laboratory investigations revealed severe proteinuria (16.2 g protein/day), microscopic hema-

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Received for publication December 1, 2014; Accepted for publication January 8, 2015

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teinemia (serum total protein 4.3 g/dL, albumin 2.4 g/dL), renal dysfunction [serum urea nitrogen 65.9 mg/dL, creatinine 3.87 mg/dL, estimated glomerular filtration rate (eGFR) 11.1 mL/min/1.73 m²] and hyperlipidemia [total cholesterol 462 mg/dL, triglycerides 275 mg/dL, high-density lipoprotein cholesterol 82 mg/dL, LDL cholesterol (calculated by the Friedwald equation) 310 mg/dL]. Plasma complement was within normal limits. The patient had no history of major diseases, and no sibling had proteinuria or hematuria.

On the seventh day of admission, a renal biopsy was performed. Glomeruli did not show any structural changes under light microscopy (Fig. 1A, B). The main pathology was in the renal tubules (Fig. 1C). Proximal tubules showed severe damage, including loss of the brush border of the proximal tubule, flattening of the epithelial cells, and detachment of cells from the basal membrane. Proteinaceous casts were seen in some tubular lumens, some of which contained cell debris. Under electron microscopy, extensive foot process effacement of the glomerular podocytes was seen, but there were no electron dense deposits (Fig. 1D). Immunofluorescence examination was negative for IgG, IgM, IgA, C3, C4 and C1q. The patient was diagnosed with MCD and acute tubular necrosis, and started steroid treatment (prednisolone 40 mg/day). Hemodialysis was performed from day 3 of admission because of anuria. There was no improvement in her renal function after 65 days of steroid therapy, and a second renal biopsy was then performed. Of the 37 glomeruli, one lobular lesion, one focal sclerosis and two tip lesions were observed (Fig. 2A, B). The pathological findings were consistent with acute tubular necrosis. Compared with the first biopsy, there was improvement in proximal tubular injury, with regeneration of the brush border and tubular cells and decreased detachment of cells from the basal membrane (Fig. 2C). The patient was diagnosed with the tip variant of FSGS.

The patient then started twice weekly LDL-A, which was performed using polysulfone hollow fiber filters (Suflux FP-05; Kaneka, Osaka, Japan) as the plasma separator and dextran sulfate cellulose columns (Liposorba LA15; Kaneka) as the LDL absorber. Approximately 3 L of plasma was treated during each LDL-A session. After six LDL-A sessions, the urine volume gradually increased and urinary protein excretion gradually decreased. After nine LDL-A sessions, hemodialysis became unnecessary, 97 days after it had been initiated. During anuria, cyclosporine was not given to the patient because of a concern that it might adversely affect ischemia in renal tubular cells. However, after recovery of the urine volume, the patient was administered cyclosporine (50 mg/day), with a gradual reduction in prednisolone. Finally, 140 days after admission, the patient was discharged without the need for renal replacement therapy (Fig. 3). Her

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Initial renal biopsy findings. All glomeruli were without any structural changes as observed with light microscopy. (A) Periodic acid-Schiff (PAS) stain, original magnification ×400. (B) Periodic acid-silver methenamine (PAM) stain, original magnification ×400. (C) Loss of the brush border of the proximal tubule, flattening of epithelial cells and detachment of cells from the basal membrane. Proteinaceous casts were seen in some tubular lumens, some of which contained cell debris. (D) Electron microscopy findings with extensive foot process effacement of glomerular podocytes. No electron-dense deposits were seen.
Figure 2. Second renal biopsy findings. Focal and segmental sclerosis involving a small portion of the glomerular tuft with adhesion to the Bowman capsule at the origin of the proximal tubule; tip lesion variant of focal segmental glomerular sclerosis (arrows). (A) PAM stain, original magnification ×400. (B) PAM stain, original magnification ×1,000. (C) Regeneration of the brush border in proximal tubular cells and regeneration of tubular cells were observed. PAS stain, original magnification ×400.

urine protein, serum creatinine and eGFR values at discharge were 1.1 g/day, 0.96 mg/dL and 50.9 mL/min/1.73 m², respectively. Her serum albumin concentration was 2.3 mg/dL at discharge, but 2 weeks later, it had improved to 3.2 mg/dL.

Discussion

In this case, FSGS was not diagnosed following the first renal biopsy. Previous reports have demonstrated the difficulty in diagnosing FSGS from only one renal biopsy in both pediatric and adult cases (5, 9). The relationship between MCD and FSGS is controversial. It is unclear whether the histologic diagnosis of FSGS is missed on an initial biopsy because of the focal nature of the lesions, or whether there is progression to FSGS, perhaps related to prolonged periods of severe proteinuria. We therefore suggest that a repeat biopsy is important in cases of drug-resistant and severe NS.

AKI in this case of NS showed features that were consistent with acute tubular injury, with interstitial inflammation and edema. It is possible that proteinuria itself may contribute to the observed tubular and interstitial damage because there is increasing evidence to suggest that exposure of proximal tubular cells to albumin overload can lead to endoplasmic reticulum stress (10) and induction of apoptosis (11). Another report showed that FSGS patients with AKI had more severe acute tubulointerstitial injury, represented by higher levels of urine N-acetyl-beta-D glucosaminidase and retinol-binding protein and higher pathological scores for acute damage (8). Our case also revealed severe tubulointerstitial damage at renal biopsy, which we considered a result of severe proteinuria. As most FSGS is drug-resistant, severe proteinuria and tubular damage can be prolonged. However, compared with the initial renal biopsy, the second biopsy showed improvement in tubular damage. We thus decided to complete a more aggressive treatment regimen.

We selected LDL-A rather than cyclosporine because cyclosporine, a calcineurin inhibitor, is known to induce nephrotoxicity as a result of acute arteriolopathy (12). LDL-A has been used as an adjunctive treatment in addition to regular medication. A prospective, observational, cohort study of LDL-A for drug-resistant NS reported that FSGS was the most frequent primary disease (52.3%) among drug-resistant NS patients (13). More than half of the drug-resistant cases showed remission after LDL-A. The study also reported that LDL-A was more effective when administered to patients within 8 weeks of NS onset than after 8 weeks (84.6% vs. 43.3%).
Several possible mechanisms have been proposed for the beneficial therapeutic effect of LDL-A including the following: reduced serum lipid levels including LDL, oxidized LDL and very low-density lipoprotein (14, 15); removal of pathogenic factors other than noxious lipids, e.g., von Willebrand factor, fibrinogen (16, 17) and thromboxane A2 (18); decreased inflammation resulting from increased endothelial nitric oxide synthase levels and decreased levels of vascular cell adhesion molecule 1 (19), platelet factor 4 on the surface of platelets (20), proinflammatory complement factors including C3a and C5 and proinflammatory cytokines [tumor necrosis factor-α, monocyte chemotactic protein-1, interferon-γ, interleukin (IL)-1α, IL-1β and IL-6] (21). A reduction in inflammation is believed to improve capillary ischemia; and improvement in the therapeutic effect of anti-proteinuric drugs, including steroids and/or calcineurin inhibitors whose bioavailability is known to be impaired under hyperlipidemic conditions (22).

Interestingly, we did not observe hyperlipidemia in the present case following LDL-A. We believe that LDL-A was effective because it removed pathogenic factors other than LDL and improved the hemodynamics. Renal ischemia and severe proteinuria can negatively affect tubular regeneration. It is possible that pathological factors other than LDL may exacerbate the renal function. In this case, LDL-A may have modified such factors.

Table details four studies with a total of 20 cases of severe renal dysfunction in patients with NS who successfully completed hemodialysis. The duration of dialysis treatment was less than 8 weeks in most cases, except in the study by Waldman et al. (9), which reported complete or partial remission in four patients after 5 to 24 weeks of therapy. Only one of the 20 cases received LDL-A (23) and other patients achieved remission with steroid and immunosuppressive therapy. Our case had a longer duration of dialysis with LDL-A compared with those described in previous reports.

In summary, a case of acute renal failure and steroid-resistant NS resulting from FSGS has been described in which LDL-A had a therapeutic benefit. This case suggests that LDL-A may represent an effective rescue treatment in patients with FSGS and long-term anuria, and warrants further investigation.
The authors state that they have no Conflict of Interest (COI).

Acknowledgement
The authors acknowledge the valuable assistance of Dr. Oka Kazumasa at Hyogo Prefectural Nishinomiya Hospital.

References