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Low-density lipoprotein apheresis in a pediatric patient with refractory nephrotic syndrome due to focal segmental glomerulosclerosis

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Abstract
Focal segmental glomerulosclerosis (FSGS) often leads to refractory nephrotic syndrome (NS). A high level of low-density lipoprotein (LDL) is a risk factor for the progression of NS. An 8-year-old girl presented with severe proteinuria refractory to steroid therapy. She was diagnosed with non-IgA diffuse mesangial proliferative glomerulonephritis. Oral prednisolone, methylprednisolone (mPL) pulse therapy, and cyclosporine and cyclophosphamide therapy failed to achieve remission. Follow-up renal biopsy revealed FSGS. Her serum level of LDL was high, and LDL-apheresis (LDL-A) was performed five times, followed by mPL pulse therapy. Urinary protein decreased from 2–4 g·day^{-1} to 0.5–1.0 g·day^{-1}. LDL-A may be beneficial in the treatment of multidrug-resistant FSGS.

Key words Low-density lipoprotein apheresis · Focal segmental glomerulosclerosis · Pediatric patient

Introduction

Focal segmental glomerulosclerosis (FSGS) often leads to severe nephrotic syndrome (NS), which is sometimes resistant to steroids or immunosuppressants and in which there is a rapid decline of renal function [1,2]. Although the pathogenesis of the disease has not been well elucidated, secondary hyperlipidemia plays a pivotal role in the progression of the renal injury [3]. Low-density lipoprotein apheresis (LDL-A) has been extended to the treatment of refractory NS due to steroid-resistant FSGS, minimal change nephropathy, membranous nephropathy, or diabetic nephropathy [4–10]. LDL-A improved abnormal lipid metabolism and reduced urinary protein loss in adult NS [4–7]. However, there have been few reports on the efficacy of LDL-A for pediatric NS [8]. We here report a pediatric patient with NS due to FSGS successfully treated with LDL-A.

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Case report

The patient was an 8-year-old girl who was 128 cm tall and weighed 29 kg. She had developed eyelid edema 3 months previously and proteinuria was noted at an annual school examination. Laboratory studies disclosed urinary protein excretion (Up) 656 mg·dl^{-1}; urinary occult blood, 3+; serum total protein (TP), 5.1 g·dl^{-1}; albumin (Alb), 2.5 g·dl^{-1}; and total cholesterol (T-cho), 399 mg·dl^{-1}. She was diagnosed with NS, and a kidney biopsy revealed non-IgA diffuse mesangial proliferative glomerulonephritis. She was treated with prednisolone 60 mg·day^{-1} for 3 weeks, while her urinary protein loss remained at 2–3 g·day^{-1}. She was transferred to our hospital for further evaluation.

On admission, urinalysis revealed Up, 243 mg·dl^{-1}; urine creatinine, (Ucr), 45.8 mg·dl^{-1}; Up/Ucr, 5.3; and protein loss, 2.6 g·day^{-1}; with sediment containing 5–9 erythrocytes and 5–9 leukocytes per high-power field. Creatinine clearance was 120 ml·min^{-1} per 1.73 m^2 body surface area. Immunoglobulin (Ig) G was 318 mg·dl^{-1}; C3, 123 mg·dl^{-1}; C4, 13 mg·dl^{-1}; CH50, 58 mg·dl^{-1}; and antinuclear antibody and anti-DNA antibody were negative. We started prednisolone (2 mg·kg^{-1}·day^{-1}) and methylprednisolone (mPL) 800 mg·day^{-1} for 3 consecutive days at 1, 2, 5, 7, and 9 weeks after admission. Cyclosporine (CyA; 80 mg·day^{-1}) was also administered at 2 weeks after admission, but failed to decrease the protein loss. We stopped CyA and it was replaced with cyclophosphamide (CPA; 50 mg·day^{-1}) and a cyclooxygenase II inhibitor (aluminum flufenamate, 250 mg·day^{-1}). Despite CPA therapy for 7 weeks, protein

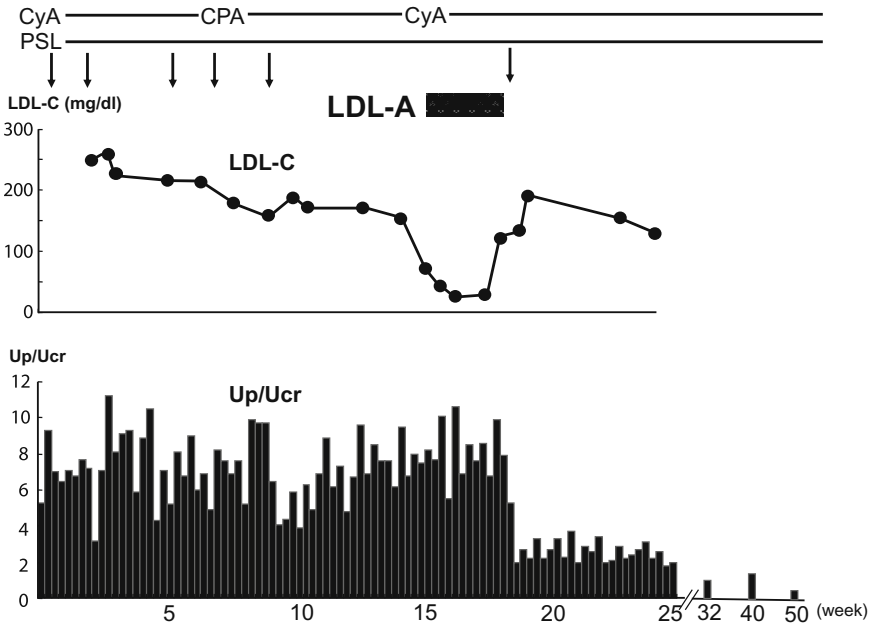

Fig. 1. The time course of steroid, cyclosporine, and cyclophosphamide therapy (*top*), low-density lipoprotein cholesterol (*LDL-C*; *middle*), and urine protein-urinary creatinine ratio (*bottom*). After low-density lipoprotein apheresis (*LDL-A*) therapy, LDL-C started to decrease and urinary protein loss gradually decreased. *Arrows* indicate steroid pulse therapy. *PSL*, *Prednisolone*; *CyA*, cyclosporine; *CPA*, cyclophosphamide; *Up*, urine protein excretion; *Ucr*, urine creatinine

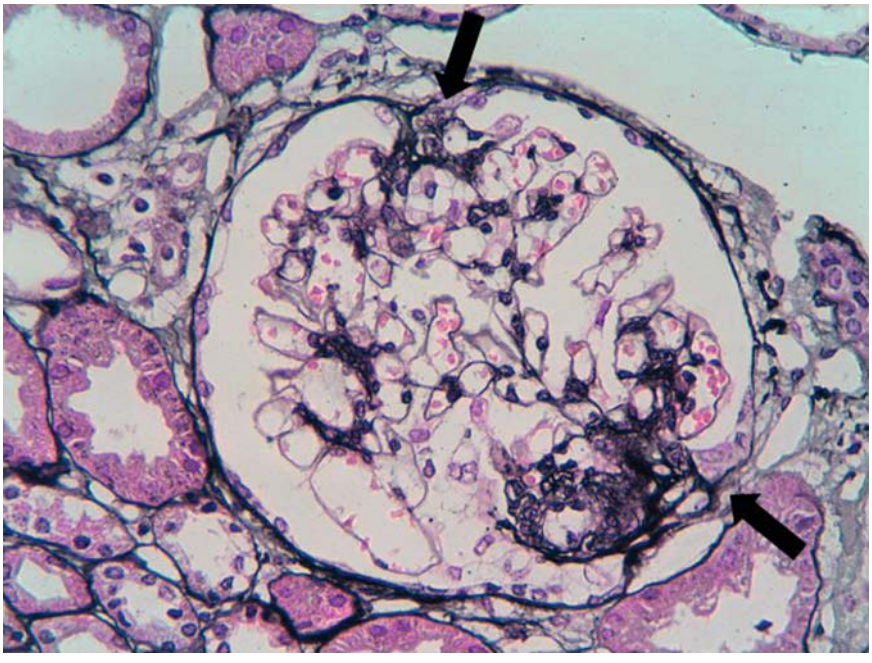

Fig. 2. Kidney biopsy specimen: microscopic analysis. Glomerulus shows segmental sclerosis with adhesion to Bowman's capsule (*arrows*). Tubular atrophy and interstitial fibrosis are absent. Periodic acid silver-methenamine (PAM), ×400

loss remained at 2–4 g·day^{-1} and Up/Ucr continued to show a value of 5–11 (Fig. 1). In week 13, she was diagnosed with FSGS by a transdermal needle biopsy of the kidney (Fig. 2). In week 15, LDL-A was started with CyA administration. After transferring the patient to an intensive care unit (ICU), we performed LDL-A, using a polysulfone hollow-fiber filter (Sulflux FPO2; Kaneka, Osaka, Japan) as a plasma separator and a dextran sulfate cellulose column (Liposorber LA-15; Kaneka) as an LDL adsorber. The volume of the extracorporeal circulation approximately 351 ml, and the line was primed with 5% albumin solution. An 8-Fr double-lumen urokinase immobilized central venous catheter (Blood Access UK-Catheter Kit, Twinend; Unitika, Hyogo, Japan) was inserted into the femoral vein. LDL-A was repeated five times in 3 weeks. The amount of plasma exchange was set at 2000 ml per session. After the completion of the LDL-A therapy, mPL 800 mg·day^{-1} was administered for 3 consecutive days. Urinary protein loss and Up/Ucr decreased to 0.5–1.0 g·day^{-1} and 1.8–3.3, respectively (Fig. 1). We kept prednisolone at 5 mg·day^{-1} and CyA at 65 mg·day^{-1}. She

was discharged on hospital day 180. At 6-month follow up, Up/Ucr remained low, at 0.6, and she did not relapse into NS.

Discussion

We have presented a pediatric patient with NS due to FSGS complicated with hyperlipidemia. Although oral prednisolone, mPL pulse therapy, and conventional doses of CyA and CPA failed to decrease urinary protein loss, LDL-A resulted in partial remission.

FSGS occurs in about 10% of children with idiopathic NS [1]. More than 80% of FSGS is steroid-resistant from the onset and even those patients who respond initially may develop secondary resistance [1]. Multiple treatment regimens, such as prolonged oral prednisone, cytotoxic drugs, CyA, or intravenous mPL pulse therapy, are employed for steroid-resistant FSGS, although it may progress to end-stage renal disease [2]. Although the pathogenesis of FSGS is not clear, secondary hyperlipidemia is implicated as a possible factor in the renal dysfunction [3]. Recently, LDL-A has been proposed as a therapeutic intervention for patients with steroid-resistant FSGS [4–8]. Muso et al. [7] reported that in adult patients with steroid-resistant NS due to FSGS or minimal change nephropathy, LDL-A ameliorated the severe proteinuria and improved renal function, along with the alleviation of hyperlipidemia, and achieved remission. Hattori et al. [8] reported that LDL-A and prednisolone therapy provided complete remission in 5 of 11 pediatric patients with steroid-resistant primary FSGS (median age at disease onset, 12 years; range, 7 to 14 years). Although the mechanism of the beneficial effects of LDL-A in patients with NS is unclear, some experiments have revealed that a reduction in oxidized LDL reduced inflammatory cytokines and chemokines and suppressed macrophage invasion into glomeruli or interstitium [7,11]. It was also reported that the adsorption of unknown factors by dextran sulfate alleviated the hypercoagulability and renal vasoconstriction [7,11]. Another possible mechanism is the enhancement of corticosteroid or CyA response by changing drug interactions after lipid removal [6,8,11]. The mPL pulse therapy after the completion of LDL-A may have contributed to the good outcome in our patient.

An appropriate time schedule of LDL-A for NS is not clear; it is commonly performed twice a week for 3 weeks and then once a week for 6 weeks [7,8,11]. In the present patient, we started LDL-A early in the course of the disease compared to other reports, and this may be a reason why no more than five sessions of LDL-A were effective in reducing the proteinuria. Her renal biopsy revealed no severe chronic tubulointerstitial lesions, such as tubular atrophy or interstitial fibrosis. The severity of tubulointerstitial fibrosis is an independent predictive factor for response to therapy and renal survival in NS patients [12]. Also, the combined drug therapy regimen may be important. Whereas a previous report used low-dose prednisolone [8], we used methylprednisolone (mPL) pulse therapy and CyA. This difference may also have affected the good outcome in our patient.

The use of therapeutic apheresis in pediatric patients is limited because of lack of cooperation, the relatively large extracorporeal volume, and the difficulties in adequate vascular access [13]. In general, when the volume of the extracorporeal circulation is lower than 15% of the patient's total blood volume, there are no significant side effects [13]. In our patient, the volume of the extracorporeal circulation was about 15% of the patient's total blood volume. Fortunately, there were no complications, such as hypotension, catheter-related infection, or thrombosis. It is desirable that the device used for LDL-A be simplified and downsized, because 60% of pediatric patients with FSGS are under 7 years of age [14].

In conclusion, we treated multidrug-resistant FSGS in a pediatric patient. LDL-A, combined with mPL pulse and CyA therapy, led to rapid amelioration of hyperlipidemia and reduction of proteinuria. LDL-A can be an alternative for pediatric patient with multidrug-resistant FSGS.

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