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Case Report

Low-Density Lipoprotein Apheresis for Proteinuria in Lupus Nephritis With Intraglomerular Foam Cells Containing Cholesterol Crystals

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A 28-year-old woman with systemic lupus erythematosus was referred to our hospital due to nephrotic-level proteinuria despite approximately 1 year of treatment with 50 to 60 mg/d of prednisolone and 100 to 150 mg/d of cyclosporine with methylprednisolone pulse therapy. Kidney biopsy showed diffuse global lupus nephritis (World Health Organization class 4-G A/C) with many intraglomerular foam cells containing cholesterol crystals. Surprisingly, proteinuria diminished after only 5 low-density lipoprotein (LDL) cholesterol apheresis sessions. This case demonstrated the potential of LDL apheresis to exhibit a remarkable effect on not only focal segmental glomerulosclerosis, but also other types of nephritis, particularly nephritis with intraglomerular foam cells.

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The proteinuria-reducing effect of apheresis of low-density lipoprotein (LDL) cholesterol in nephrotic syndromes such as focal segmental glomerulosclerosis (FSGS) has been reported. However, a precise mechanism of action has not yet been elucidated.[1] We report dramatic improvement in proteinuria by LDL apheresis in a patient with nephritic lupus nephritis with intraglomerular foam cells. The findings of this case offer valuable insight into the possible involvement of foam cells in at least some types of nephrotic syndrome, thus providing a potential mechanism for the proteinuria-reducing effect of LDL apheresis.

CASE REPORT

A 28-year-old woman was referred to our hospital with a year-long history of severe proteinuria. Systemic lupus erythematosus (SLE) with lupus nephritis had been diagnosed when she was 15 years old, and she had undergone treatment with methylprednisolone pulse therapy. Because she developed frequent relapses of lupus nephritis in addition to other types of SLE complications (eg, lupus dermatitis, hemolytic anemia, and thrombocytopenia), 4 sessions of methylprednisolone pulse therapy had been administered in combination with various immunosuppressive agents, such as oral prednisolone, cyclosporine (CsA), cyclophosphamide, and mizoribine. Approximately 1 year before presentation, our patient experienced recurrence of nephrotic lupus nephritis with hypocomplementemia and hemolytic anemia. Thus, methylprednisolone pulse therapy and the subsequent year-long maintenance therapy (50-60 mg/d of oral prednisolone and 100-150 mg/d of CsA) appeared to have been ineffective against her proteinuria.

Upon admission, the patient had marked periorbital and leg edema. Prior medications included prednisolone (60 mg), CsA (150 mg), atorvastatin (20 mg), telmisartan (80 mg), amlodipine (5 mg), and furosemide (20 mg). Blood tests showed the following values: white blood cell count, $14 \times 10^3/\mu L$; hemoglobin, 9.6 g/dL; platelets, $248 \times 10^3/\mu L$; albumin, 2.0 g/dL; creatinine, 0.82 mg/dL (corresponding to estimated glomerular filtration rate of 69 mL/min/1.73 m^2 as calculated by the Japanese glomerular filtration rate estimation equation[2]); triglycerides, 411 mg/dL; LDL cholesterol, 465 mg/dL; high-density lipoprotein cholesterol, 46 mg/dL; lipoprotein(a), 29.9 mg/dL; hemoglobin A_{1c}, 5.6%; immunoglobulin G (IgG), 230 mg/dL; IgA, 118 mg/dL; IgM, 77 mg/dL; C3 complement, 67.9 mg/dL; C4 complement, 12.6 mg/dL; immune complex (C1q) undetected; antinuclear antibody, 50 (reference range, <20); and anti–double-stranded DNA antibody, 11 (reference, <12) IU/mL. Urinalysis showed protein (4.7 g/d), 1 to 4 erythrocytes/high-power field, 0 to 1 leukocyte/high-power field, 1 to 3 hyaline casts/low-power field, and 1 to 3 oval fat bodies/low-power field. Creatinine clearance was 72 mL/min/1.73 m^2, and the selectivity index of urinary protein was 0.45.

The kidney biopsy specimen showed 7 global sclerotic glomeruli and 5 fibrous crescents among the 40 glomeruli obtained. Almost all surviving glomeruli showed endocapillary proliferation, increased matrix and mesangial cellularity, and thickened capillary walls. In addition, foam cell formation was observed in about half the glomeruli, mainly in the endocapillary location (Fig 1A). No segmental sclerotic lesions were observed. Inclusion of lipids in the foam cells was confirmed by Oil Red-O staining (Fig 1B). In the interstitium, mild focal lymphocytic infiltration with a few foam cells was observed, and focal interstitial fibrosis was present around the global sclerotic glomeruli. Strong coarse granular deposition of IgG and C1q (Fig 1C) and

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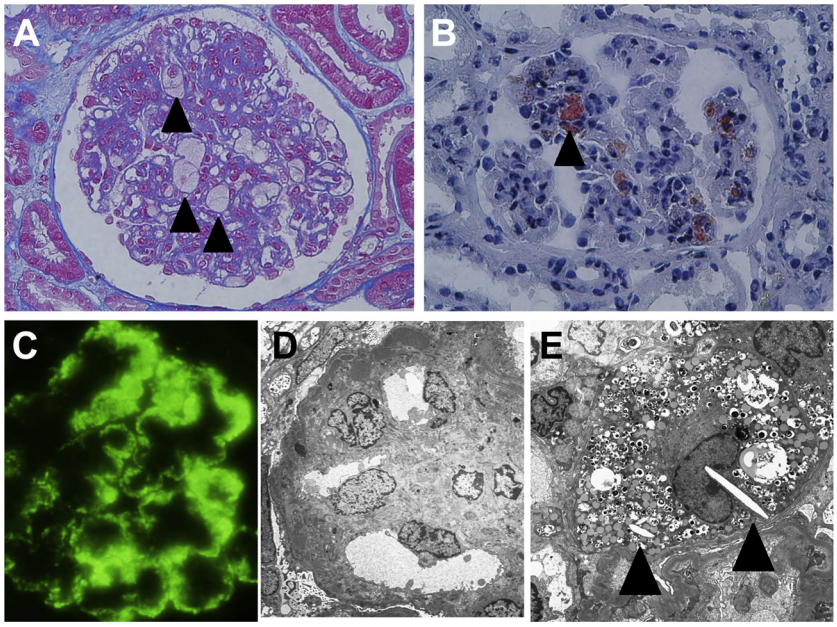

Figure 1. Microscopic findings. (A) A nonsclerotic glomerulus with intracapillary foam cells (arrowheads) (azan trichrome stain; original magnification, ×200). (B) Intraglomerular foam cells (arrowhead) (Oil Red-O stain; original magnification, ×200). (C) Immunofluorescent staining for C1q (original magnification, ×200). (D) Double contour with subendothelial electron-dense deposits (electron microscopy; original magnification, ×6,000). (E) A foam cell including cytosolic cholesterol crystals (arrowheads) (electron microscopy; original magnification, ×3,000).

moderate deposition of IgA, IgM, and C3 were observed along the capillary walls and mesangial lesions using immunofluorescence microscopy. Electron microscopy revealed subendothelial electron-dense deposits and double contours of basement membranes (Fig 1D), in addition to intraglomerular foam cells containing cholesterol crystals (Fig 1E). Based on these observations, diffuse global lupus nephritis (World Health Organization class 4-G A/C) with intraglomerular foam cells was diagnosed.

Although serologic SLE activity was considered low (based on autoantibody titers and complement levels), additional treatment was required to improve nephrosis. Because 50 to 60 mg of prednisolone and 100 to 150 mg of CsA had been administered for approximately 1 year, increasing the doses of these immunosuppressive agents was unlikely to have much effect on the nephrosis. Therefore, the patient underwent LDL apheresis (LIPOSORBER LA-40; Kaneka; 4,500 mL of plasma processed per session, 1-2 sessions per week) due to elevated blood LDL cholesterol levels and many intraglomerular foam cells, although there have been few reports describing LDL apheresis for the treatment of lupus nephritis. After 2 sessions of LDL apheresis, urinary protein levels decreased, an effect that was even more dramatic as treatment continued; after only 5 sessions, urinary protein decreased to 0.2 g/d, and LDL apheresis was stopped (Fig 2A). Serum lipids were measured before and after each LDL apheresis session, with noticeable decreases observed in LDL cholesterol and lipoprotein(a) levels (Fig 2B). The patient was discharged and daily doses of prednisolone (30 mg), CsA (150 mg), atorvastatin (20 mg), telmisartan (80 mg), amlodipine (5 mg), lansoprazole (30 mg), and alendronate (5 mg) were prescribed.

Subsequent urinary protein and LDL cholesterol values remained low (~0.1 g/d and <100 mg/dL, respectively). Three years after stopping LDL apheresis, the patient gave birth after an uneventful pregnancy. Her proteinuria and SLE are controlled with daily prednisolone (5 mg), CsA (100 mg), atorvastatin (10 mg), and telmisartan (40 mg).

DISCUSSION

Renal foam cells are observed mainly in the interstitium in several glomerular diseases such as FSGS, membranous nephropathy, and Alport syndrome.[3,4] Intraglomerular foam cells are observed infrequently in sclerotic lesions and endocapillaries; these types of cells are speculated to play a role in the formation of segmental sclerosis, especially in FSGS.[3] Meanwhile, in patients with lupus nephritis, the presence of renal foam cells has yet to be reported. Animal experiments and clinical observations suggest that elevated levels of serum LDL and very-low-density lipoprotein (VLDL) cholesterol, which are associated with nephrosis, have an important role in foam cell formation.[5] However, several reports have demonstrated that nephrotic syndrome and hyperlipidemia are not essential for renal foam cell formation. Therefore, the mechanism underlying foam cell formation remains controversial.[3]

In contrast, the mechanisms underlying macrophage foam cell formation in arteriosclerosis have been well studied.[6] Macrophages internalize LDL and VLDL cholesterol, as well as oxidized LDL cholesterol, by LDL receptors and scavenger receptors. When internalized, lipoproteins are delivered to the endoplasmic reticulum and stored in cytosolic droplets in an esterified form. The accumulation of intracellular cholesterol activates the cholesterol efflux system, and stored cholesterol esters are hydrolyzed and transferred extracellularly to maintain constant intracellular cholesterol levels. However, when a macrophage is stimulated by proinflammatory cytokines, the cholesterol efflux system is inhibited and free cholesterol accumulates, transforming the macrophage into a foam cell. The foam cell secretes various chemical mediators, promoting the development of arteriosclerosis. Similarly, intraglomerular foam cells may play a role in glomerulosclerosis.[7] Furthermore, electron microscopy analysis revealed the formation of intracellular