INTERNAL MEDICINE

□ CASE REPORT □

Umbilical Cord Blood Transplantation-associated Nephrotic Syndrome Successfully Treated by Low-density Lipoprotein Apheresis

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Abstract

The development of nephrotic syndrome (NS) after umbilical cord transplantation (UBT) has been reported in only four cases to date. We herein report the case of a 50-year-old woman who developed NS 94 days after UBT. She fell into oliguria and required dialysis. A kidney biopsy revealed focal and segmental glomerulosclerosis. Although glucocorticoid monotherapy did not improve her condition, the addition of low-density lipoprotein (LDL) apheresis resulted in remission of NS, a drastic improvement in her renal function, and withdrawal from dialysis. To the best of our knowledge, this is the first report of UBT-associated NS treated with LDL apheresis.

Key words: umbilical cord blood transplantation, nephrotic syndrome, LDL apheresis, focal segmental glomerulosclerosis

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Introduction

The development of nephrotic syndrome (NS) after bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT) is rare, with a reported incidence rate of 0.37-1.03% (1, 2). The development of NS after umbilical cord blood transplantation (UBT) is considered to be less frequent, and only four cases have been reported thus far. Glucocorticoid monotherapy successfully achieved remission of proteinuria in three cases (3-5), while multiple immunosuppressive agents were required for complete remission of proteinuria in one case (6). However, the number of patients undergoing UBT is increasing in adults, as well as in children. Therefore, cases with rare complications, including UBT-associated NS, are expected to increase in the future.

We herein report a case of UBT-associated NS successfully treated with glucocorticoid therapy and low-density lipoprotein (LDL) apheresis. This is the first reported case of UBT-associated NS successfully treated with LDL apheresis.

Case Report

Seven months prior to admission, a 50-year-old woman was referred to our hospital for an evaluation of dyspnea and palpitation. Her white blood cell count in the peripheral blood was elevated (61,900/μL). Bone marrow aspiration (BMA) revealed hypercellular bone marrow with 51% blasts, and the patient was diagnosed with acute myeloid leukemia (AML). The subtype of AML classified by the

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Table 1. Laboratory Tests on Admission.

Complete blood count			Blood chemistry			Serologiacl test		
WBC	3,700	/μL	TP	4.4	g/dL	CRP	0.56	mg/dL
RBC	263×10^4	/μL	Alb	1.6	g/dL	ANA	1:40	
Hb	8.4	g/dL	UA	9.0	mg/dL	IgG	1,066	mg/dL
Ht	26	%	BUN	42	mg/dL	IgA	117	mg/dL
PLT	5.9×10^4	/μL	Cre	2.84	mg/dL	IgM	294	mg/dL
venous blood gas			eGFR	14.9	mL/min/1.73m^2	C3	69	mg/dL
pH	7.326		Na	126	mEq/L	C4	8	mg/dL
pCO_2	27.1	mmHg	K	5.0	mEq/L	CH50	<10	U/mL
HCO_3	13.8	mmol/L	Cl	98	mEq/L	MPO-ANCA	(-)	
Anion gap	18.7	mmol/L	cCa	10.0	mg/dL	PR3-ANCA	(-)	
Urinary test			IP	6.8	mg/dL	HBs-Ag	(-)	
Urinalysis	Protein	(4+)	TSAT	46	%	HCV-Ab	(-)	
	Occult blood	(3+)	Ferritin	3,179	ng/mL			
UPCR	19,581	mg/gCre	LDH	215	U/L			
RBC	>100	HPF	T-Cho	272	mg/dL			
NAG	80.4	U/gCre	TG	582	mg/dL			
α1MG	109.8	mg/gCre	Glu	131	mg/dL			
SI	0.22		HbA1c	4.3	%			

α1MG: α1-microglobulin, ANA: anti-nuclear antibody, HPF: high-power field, NAG: N-acetyl-β-glucosaminidase, TSAT: transferrin saturation, UPCR: urine protein/creatinine ratio, SI: selectivity index

French-American-British Classification was M4 or myelomonocytic leukemia. She received an initial cycle of induction therapy [12 mg/m^2/day of idarubicin on days 1 to 3, 100 mg/m^2/day of cytarabine daily for seven days], however, complete remission was not achieved. Therefore, re-induction therapy was performed [12 mg/m^2/day of idarubicin on days 1 and 2, 100 mg/m^2/day of cytarabine daily for five days], however, the patient again did not achieve remission. Moreover, delayed recovery of normal hematopoiesis prompted the patient to undergo transplantation. Her basal kidney function was normal and urine abnormality was absent before transplantation. Three months prior to this admission, after being conditioned with cytarabine (100 mg/m^2/day for three days), followed by intravenous busulfan (60 mg/kg) and cyclophosphamide (60 mg/kg for two days), human leucocyte antigen (HLA)-DR one-mismatched UBT was performed (day 0). Graft-versus-host disease (GVHD) prophylaxis was performed with cyclosporine (CsA) and methotrexate. The patient received 2.9×10^7/kg total nucleated cells and 0.73×10^5 CD34$^+$ cells. On day 5, glucocorticoid pulse therapy was performed against hemophagocytic syndrome. On day 29, engraftment was achieved. A skin rash appeared on the hands and forearms on day 44, which was diagnosed as acute GVHD because a skin biopsy revealed the infiltration of perivascular lymphocytes in the superficial dermis. The rash disappeared with topical steroid treatment. No other GVHD was observed. BMA on day 60 pathologically confirmed that she remained in remission. The dose of glucocorticoid was gradually tapered and it was discontinued on day 88. The dose of CsA was also gradually decreased to 40 mg/day. Under a diagnosis of cytomegalovirus (CMV) infection, the patient was treated with foscarnet (PFA) from day 57 to day 70.

On day 88, the patient noticed a reduction in her urine volume. After discharge on day 90, peripheral edema appeared and worsened; therefore, she was admitted to our hospital on day 94 after UBT due to general malaise and a decreased urine volume. On physical examination, her vital signs were normal. No lymphadenopathy or organomegaly was noted. Neither fine nor coarse crackles were audible in the lung field, whereas pitting edema of the lower extremities together with 5 kg of body weight gain was present. Rashes were found on the bilateral forearm, which had been suspected as GVHD, however, there was no sign of GVHD in the liver or gut. Laboratory tests, which are presented in Table 1, revealed a nephrotic status: urinary protein of 19 g/gCre, serum total protein of 4.4 g/dL, serum albumin of 1.6 g/dL, and total cholesterol of 272 mg/dL. On a urinalysis, microscopic hematuria (>100/high-power field), hyaline casts, granular casts, epithelial casts, and waxy casts were detected. Other pertinent findings, including an elevated serum urea nitrogen concentration of 42 mg/dL (15 mmol/L of urea), serum creatinine concentration of 2.8 mg/dL (248 μmol/L) and a decreased estimated glemerular filtration rate (eGFR) of 14.9 mL/min/1.73 m^2, indicated acute kidney injury.

A kidney biopsy was subsequently performed. Of the 23 glomeruli, light microscopy showed segmental sclerosis around the vascular pole in one glomerulus and global sclerosis was observed in two glomeruli. There were slight hyalinosis of smooth muscle cells in the afferent arterioles and isometric vacuolation of the proximal straight tubules, which were considered to be a side effect of previous treatment with CsA. Although mild infiltration of lymphocytes and plasma cells was observed around the tubules, there was no obvious lymphocytes infiltration in the glomeruli. Immunofluorescence microscopy revealed positive staining for IgM throughout the mesangial area. Under electron microscopy, foot process effacement of the glomerular podocytes was observed, while electron dense deposits were absent (Fig. 1). Subendothelial edema was observed, which could imply endothelial damage. According to these findings, the patient was diagnosed with focal and segmental glomerulosclerosis (FSGS), perihilar variant. After the kidney biopsy,

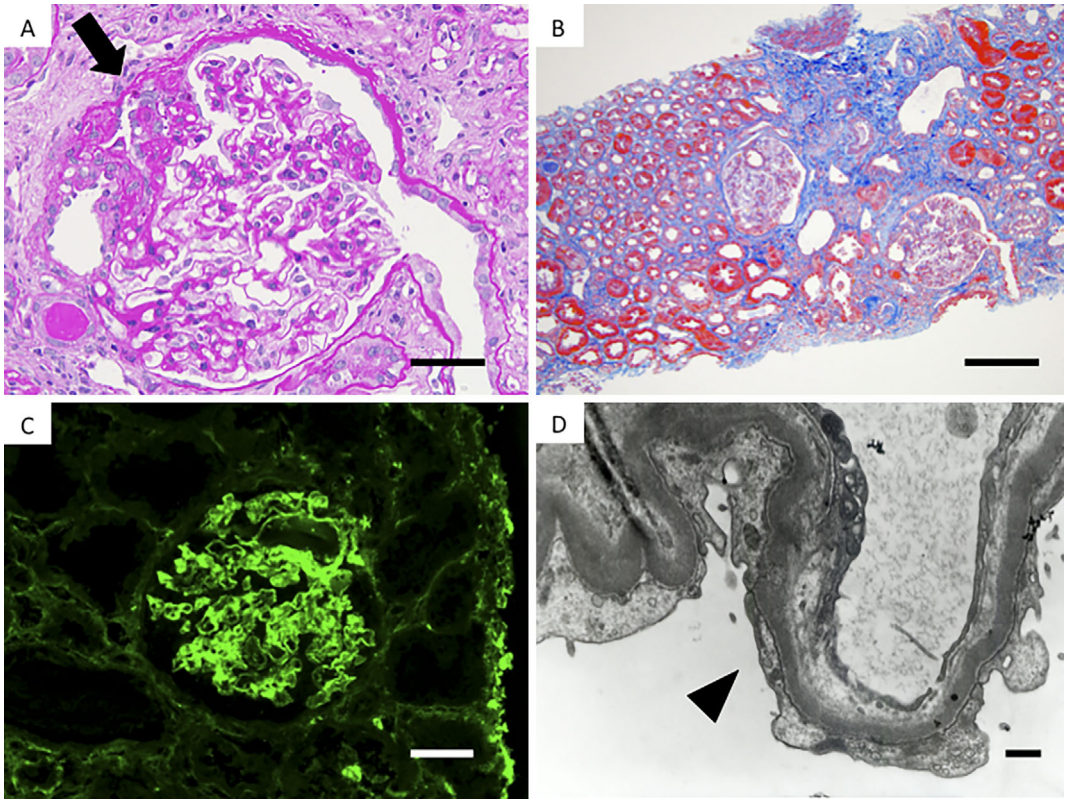

Figure 1. **(A) A light microscopic examination demonstrates segmental sclerosis around the vascular pole (arrow; Periodic acid-Schiff stain, scale bar=50 μm). (B) A light microscopic examination demonstrates focal fibrosis (Azan stain, scale bar=200 μm). (C) Immunofluorescence staining demonstrates the presence of IgM throughout the mesangial area (scale bar=100 μm). (D) Electron microscopy shows foot process effacement of the glomerular podocytes (arrowhead; scale bar=0.5 μm).**

glucocorticoid pulse therapy (methylprednisolone 1,000 mg/day for 3 days) was immediately started, followed by conventional prednisolone therapy (45 mg/day, equivalent to 1 mg/kg/day). The clinical course of the patient is shown in Fig. 2. As her renal function deteriorated, hemodialysis therapy was required from hospital day 4. Her proteinuria and renal function did not improve and massive ascites appeared, then LDL apheresis was initiated on hospital day 26. No other immunosuppressant was added because such administration could attenuate the graft versus leukemia effect (7, 8). The level of LDL cholesterol was 261 mg/dL before beginning LDL apheresis, and it decreased to 54 mg/dL after several sessions of LDL apheresis. The patient's proteinuria gradually reduced with an increase in urine volume, and massive ascites gradually decreased beginning at hospital day 38. She was able to discontinue hemodialysis on hospital day 44. The patient underwent LDL apheresis 12 times. Her urinary protein gradually decreased to 1.6 g/gCre, and the serum creatinine level returned to normal (0.55 mg/dL, 48.6 μmol/L) when she was discharged on hospital day 82. During the admission, neither relapse of AML nor adverse events of LDL apheresis were observed.

Discussion

Hematopoietic stem cell transplantation (HSCT) is broadly undertaken with the aim of a complete cure of hematopoietic malignancies. HSCT is classified into three categories according to the source of transplanted cells: BMT, PBSCT and UBT. Renal dysfunction after HSCT is common, and its causes include conditioning therapy (radiation, chemotherapy), calcineurin inhibitor use, infection, and GVHD. According to a previous study, the incidence rate of acute kidney injury was 30-50%, while that of chronic kidney disease was 17.5-66% (9). In contrast, the development of NS after HSCT is uncommon and the incidence rate was reported to be 0.37-1.03% in adults (1, 2). Membranous nephropathy (61%) was the most common histological finding, followed by minimal change disease (22%). Other histologic findings, such as FSGS in our case and IgA nephropathy, were reported in a few cases (10, 11). The complete remission rates are dependent on the pathological findings. Only 27% of patients with membranous nephropathy achieved complete remission, compared to 90% of patients with minimal change disease (11). However, no report has discussed the long-term prognosis of HSCT-associated NS, and the majority of case reports do not refer to the long-term follow-up.

Chronic GVHD is the most common late complication of HSCT. It appears in 40-80% of all patients and leads to elevated morbidity and mortality (12). The main components in the pathogenesis of GVHD are donor T-cell activation and

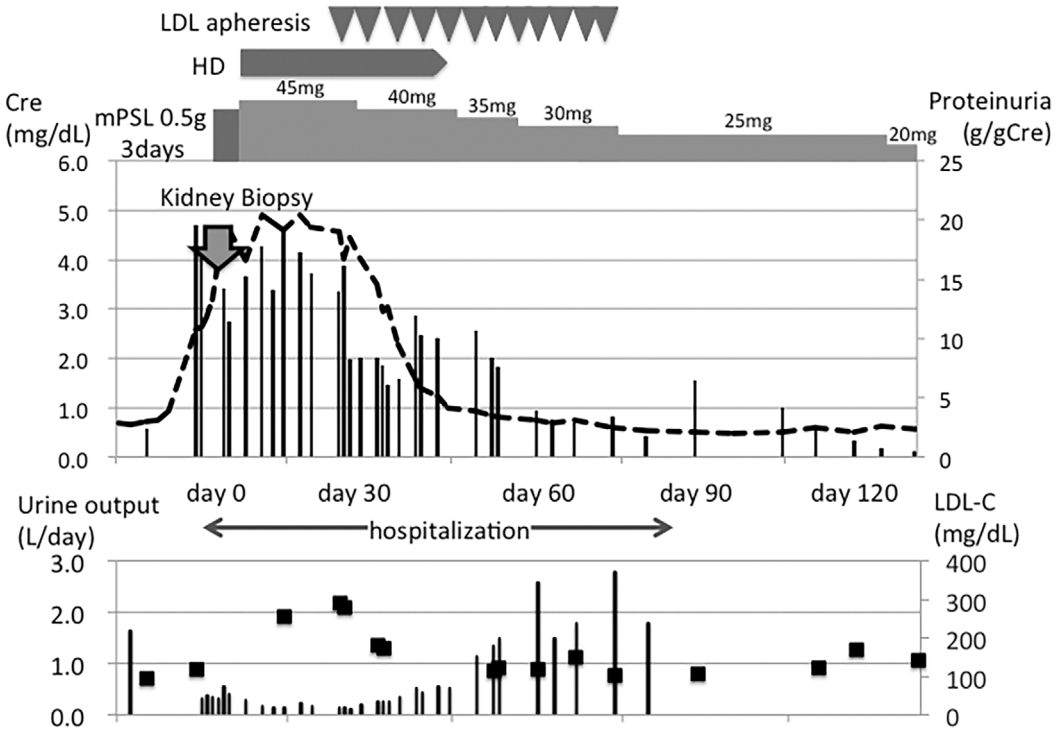

Figure 2. **The patient's clinical course. The patient's levels of serum creatinine (dashed line) are shown against treatment and several clinical parameters: daily urine protein excretion (upper bar graph), urine output (lower bar graph) and levels of LDL (closed squares). HD: hemodialysis, mPSL: methylprednisolone, PSL: prednisolone**

proliferation. Therefore, one of the pathological characteristics of GVHD is apoptosis accompanied by lymphocytes infiltration (13). Although renal involvement secondary to chronic GVHD is not common (14, 15), NS after HSCT appears to be associated with GVHD. This is likely because NS tends to develop after the discontinuation or a dosage decrease of immunosuppression therapy (16), and immunological abnormality is considered to be a cause of NS. The pathological characteristics of GVHD in the kidney remain unclear thus far, however, similar to GVHD in other organs, the infiltration of lymphocytes may also be related to renal GVHD. Several risk factors have been reported, including previous irradiation, CMV seropositivity, advanced age of the donor and/or the recipient, allo-HSCT from the peripheral blood, sex incompatibility between the donor and the recipient, and a personal history of acute GVHD (2). Luo et al. (1) also reported that the number of regulatory T cells was lower in post-transplantation NS patients compared to non-NS patients.

NS is considered to be less common after UBT than after BMT or PBSCT. This fact may be explained by a relatively low risk of GVHD in UBT compared to that in BMT and PBSCT (17). Only four cases, three cases in children and one case in adults, have been reported thus far (Table 2), therefore, our case is the second case of adult UBT-associated NS. Complete remission of proteinuria was achieved by glucocorticoid monotherapy in three cases (3-5), whereas one case (6) was refractory to multiple immunosuppression therapy with glucocorticoid, CsA and mizoribine. Rituximab was finally administered and proteinuria successfully improved four months later. The present case is similar to this refractory case in terms of FSGS and the ineffectiveness of glucocorticoid monotherapy. LDL apheresis could be performed in the present case because the patient was an adult and could endure LDL apheresis. Sustained proteinuria and severe renal dysfunction subsequently improved, despite an extended dialysis-dependent duration as long as five weeks. In our case, primary FSGS could be considered to be a differential diagnosis. However, we speculate that the most likely cause was UBT-associated and GVHD-related secondary FSGS according to the following points: the development of NS immediately after the reduction of GVHD prophylaxis, lymphocyte infiltration observed in the kidney, and the existence of skin GVHD.

LDL apheresis was originally established as a method to correct dyslipidemia specifically for familial hyperlipidemia (18, 19). The treatment is now a useful therapeutic option for a wide spectrum of disease: peripheral artery disease, ischemic heart disease, sudden deafness, retinal ischemia, and acute pancreatitis. It is also effective for refractory FSGS, and the hypothetical mechanisms of LDL apheresis are as follows: a direct effect of lipid absorption, vasodilatory and anticoagulant effects by absorption of various pathogenic factors, and enhancement of the immunosuppressant response by ameliorating intracellular drug transport (20). Seconi et al. (21) and Luo et al. (1) previously re-

Table 2. Cases of Nephrotic Syndrome after Umbilical Cord Blood Transplantation.

Age	Time of onset after Tx (months)	Change of immunosuppression therapy	Histological finding	Treatment	Time to remission (weeks)	Reference
6yr	2	FK506, intravenous to internal use.	(ND)	GC	3	3
12yr	6	CsA was reduced.	MCD	GC pulse	2	4
45yr	3.5	MMF was discontinued.	MCD	GC	4	5
9mth	4	CsA was reduced.	MCD or FSGS	GC pulse, increase CsA, add MZR, add RTX	16	6
50yr	**3**	**GC and CsA was reduced.**	**FSGS**	**GC pulse, add LDL apheresis**	**12**	**(our case)**

CsA: cyclosporine, FK506: tacrolimus, FSGS: focal and segmental glomerurosclerosis, GC: glucocorticoid, LDL: low-density lipoprotein, MCD: minimal change disease, MMF: mycophenolate mofetil, MZR: mizoribine, ND: no data, RTX: rituximab, Tx: transplantation

ported that the levels of interferon (IFN)-γ and tumor necrosis factor (TNF)-α were elevated in posttransplantation NS. LDL apheresis was reported to decrease the levels of glomerular permeability factors (22), IFN-γ (23), and LDL, and may help to decrease proteinuria (24). In our case, we cannot deny the possibility that the improvement in the patient's condition may have resulted from a therapeutic effect of glucocorticoid and that the appearance of its effect accidentally coincided with the initiation of LDL apheresis. However, we consider that the improvement in the renal function was likely caused by the effect of LDL apheresis because her proteinuria did not change for approximately one month, despite the administration of glucocorticoid.

PFA was administered to our patient for the treatment of CMV infection. PFA has been reported to cause NS according to its precipitation (25, 26). However, we speculate that PFA did not contribute to her kidney disease for two reasons. First, NS occurred 18 days after the cessation of PFA. NS with elevated serum creatinine levels developed during PFA administration in the previous reports. Second, crystal precipitation was absent both in the kidney specimen and urine sediment.

In conclusion, we reported the first case of UBT-associated NS successfully treated with glucocorticoid therapy and LDL apheresis. Close monitoring of the renal function and a urinalysis is recommended for patients who undergo HSCT. In addition to glucocorticoid therapy or other immunosuppressive therapy, LDL apheresis may be a promising therapeutic tool for UBT-associated NS or HSCT-associated NS.

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

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