INTERNAL MEDICINE

□ CASE REPORT □

Hematopoietic Stem Cell Transplantation Nephropathy Associated with Chronic Graft-versus-Host Disease without Extrarenal Involvement

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Abstract

A 30-year-old woman with myelodysplastic syndrome underwent allogeneic hematopoietic stem cell transplantation (HSCT) derived from her HLA-matched sister six years previously. She received preconditioning total body irradiation with renal shielding and was subsequently administered cyclosporin A (CyA) as prophylaxis against graft-versus-host disease (GVHD). Four months after HSCT, asymptomatic proteinuria and glomerular hematuria developed during CyA tapering without obvious extrarenal involvements of GVHD, and persisted for six years. A renal biopsy revealed endothelial injury in the glomeruli, and the deposition of C4d was detected diffusely on glomerular capillaries and focally on peritubular capillaries, suggesting that nephropathy involved antibody- or complement-associated immune reactions.

Key words: hematopoietic stem cell transplantation (HSCT), nephropathy, graft-versus-host disease (GVHD), C4d

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Introduction

Hematopoietic stem cell transplantation (HSCT) involves the transplantation of multipotent hematopoietic stem cells and includes peripheral blood stem cell transplantation (PBSCT), bone marrow transplantation, and umbilical cord blood transplantation. This therapy is annually performed for approximately 50,000 patients with various hematological diseases (1), but may result in kidney injury, known as HSCT nephropathy.

HSCT nephropathy comprises two different types (2). One type develops in the early stage within three months of HSCT for various reasons such as sepsis, hepatorenal syndrome, or the drugs administered. The other type develops more than three months after HSCT and is caused by radiation, calcineurin inhibitors (CNI), or graft-versus-host disease (GVHD), which is HSCT nephropathy in a narrow sense (3).

We herein report a case of HSCT nephropathy that may have been caused by GVHD without obvious extrarenal involvement.

Case Report

A 30-year-old woman was diagnosed with myelodysplastic syndrome (refractory anemia with excess blasts-2 with monosomy 7) and underwent allogeneic PBSCT from her HLA-matched sister six years previously. Prior to PBSCT, she had a normal renal function and did not present with either proteinuria or hematuria. She had no previous history of renal disease, hypertension, or other diseases, such as eclampsia.

Her preconditioning regimen for PBSCT was cyclophosphamide (60 mg/kg/day for 2 days) and 5 Gy of total body irradiation with partial shielding for the kidneys. Cyclosporin A (CyA) and methotrexate (10 mg/kg) were administered for a short term as prophylaxis against GVHD.

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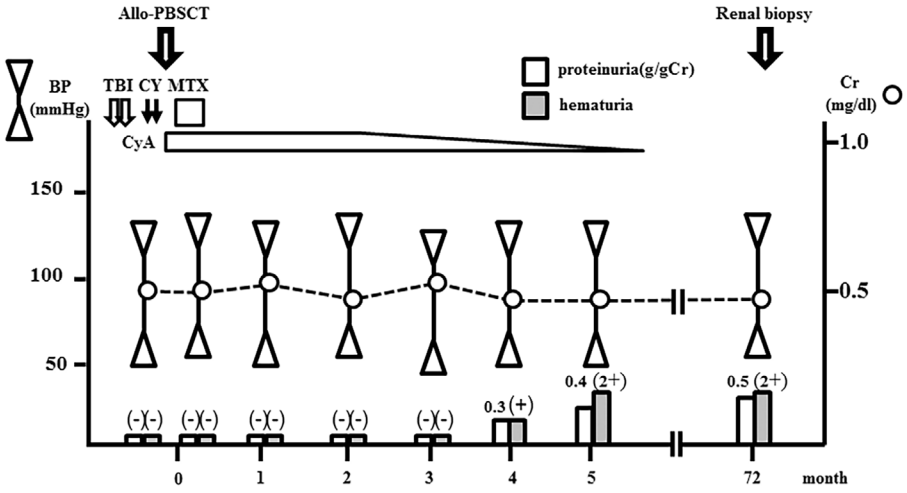

Figure 1. **Clinical course. Allo-PBSCT: allogeneic peripheral blood stem cell transplantation, BP: blood pressure, Cr: serum creatinine, CY: cyclophosphamide, CyA; cyclosporin A, MTX: methotrexate, TBI: total-body irradiation**

Table. **Laboratory Data on Admission.**

Peripheral blood		Na	138mEq/L	Urinalysis	
WBC	5800/μL	K	4.1mEq/L	Gravity	1.013
RBC	456x10^4/μL	Cl	101mEq/L	pH	6.0
Hb	12.4g/dL	Serological tests		Protein	+
Ht	38.9%	IgG	930mg/dL	Occult blood	2+
RBC fragmentation	-	IgA	80mg/dL	Sediments	
Plt	28.2x10^4/μL	IgM	59mg/dL	Dysmorphic RBC	20-29/HPF
		C3	117mg/dL	Cast	-/HPF
Blood chemistry		C4	25mg/dL	Urinary chemistry	
TP	7.4g/dL	CH50	50U/mL	TP	0.5g/gCr
AST	30IU/L	Anti-nuclear antibody	-	NAG	6.1U/gCr
ALT	18IU/L	MPO-ANCA	-	β2microglobulin	190μg/gCr
LDH	146IU/L	PR3-ANCA	-		
T-bil	0.71mg/dL	Anti-GBM antibody	-		
BUN	16.6mg/dL	HBs antigen	-		
Cr	0.51mg/dL	Anti-HCV antibody	-		

NAG: N-acetyl-β-D-glucosaminidase

CyA was initially administered intravenously (3 mg/kg/day), and was then switched to an oral form. The dose of CyA was adjusted after monitoring serum levels to maintain a trough level between 150 and 250 ng/mL.

However, asymptomatic proteinuria and glomerular hematuria appeared during CyA tapering four months after PBSCT and persisted for six years without clinical manifestations of GVHD (Fig. 1). No abnormalities were detected in the clinical or laboratory findings, except for abnormal urinalysis results (Table). Other laboratory findings revealed that the secondary causes of the urinary abnormality such as autoimmune disease or infection were negative. She was thus admitted to our hospital for a renal biopsy.

Light microscopy showed swelling of endothelial cells in glomerular capillaries, mesangial cell proliferation, and double-contoured glomerular basement membrane (Fig. 2A-C). CD34 staining revealed narrowing of the glomerular capillaries (Fig. 2D). A few $CD3^+$ T cells were detected in the glomeruli (Fig. 2E). Furthermore, slight infiltration of mononuclear cells, primarily $CD3^+$ T cells, was detected in the peritubular capillaries and tubules (Fig. 2F-H). In the interlobular and arcuate arteries, some irregular thick lesions were found in the intima with edema and an accumulation of mucoid-like materials without elastosis or cellular components (Fig. 2I-K). Under immunofluorescence microscopy, positive staining for IgM, C3, and C1q was

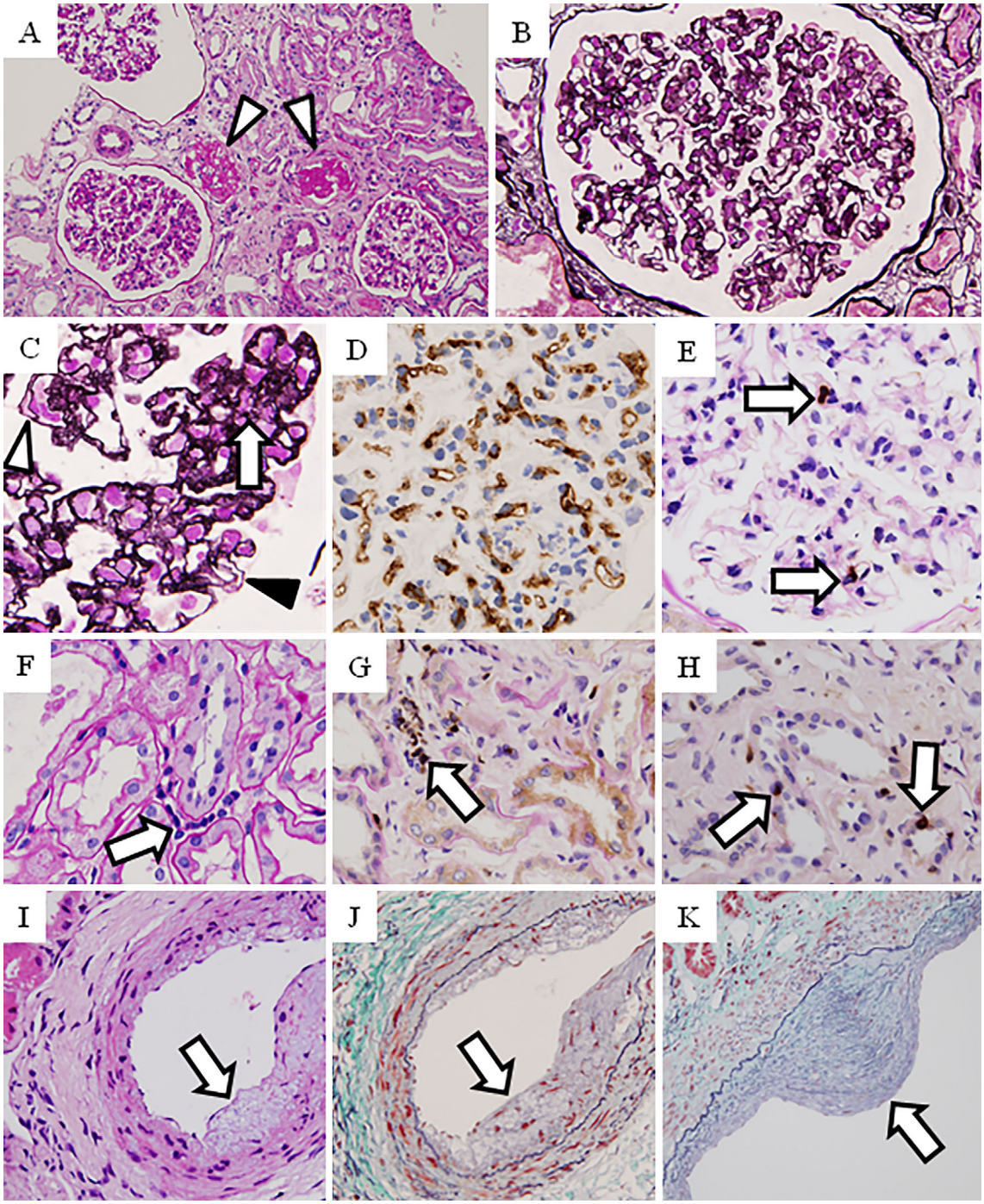

Figure 2. **Findings of the renal biopsy samples. In the renal biopsy samples, 40 glomeruli were observed, 6 of which had deteriorated (arrowheads in A; PAS stain 200×). The glomeruli showed mild hypertrophy and increased numbers of small capillary lumens with irregular thickening of the GBM (B: PAM stain 600×). The glomeruli also showed swollen endothelial cells in the glomerular capillaries (open arrowhead in C), double-contoured GBM (closed arrowhead in C), and mesangial cell proliferation (arrow in C) in the glomeruli (C: PAM stain 800×). CD34 staining revealed narrowing of the glomerular capillaries (D: CD34 stain 800×). In the glomeruli, a few $CD3^+$T cells (arrows in E) were noted (E: CD3 stain 800×). According to the results obtained for the tubulointerstitium, slight infiltration of mononuclear cells (arrow in F), primarily $CD3^+$T cells, was noted in the peritubular capillaries (arrow in G) and tubules (arrows in H) (F: PAS stain 600×; G, H: CD3 stain 600×). In interlobular arteries, irregular thickening of the intima was evident with edema and the accumulation of mucoid-like materials (arrow in I), without elastosis or cellular components (arrow in J). In addition, irregular thickening of the intima (arrow in K) was evident in arcuate arteries without elastosis (I: Hematoxylin and Eosin staining 600×; J, K: Elastic Masson-Goldner stain 600×)**

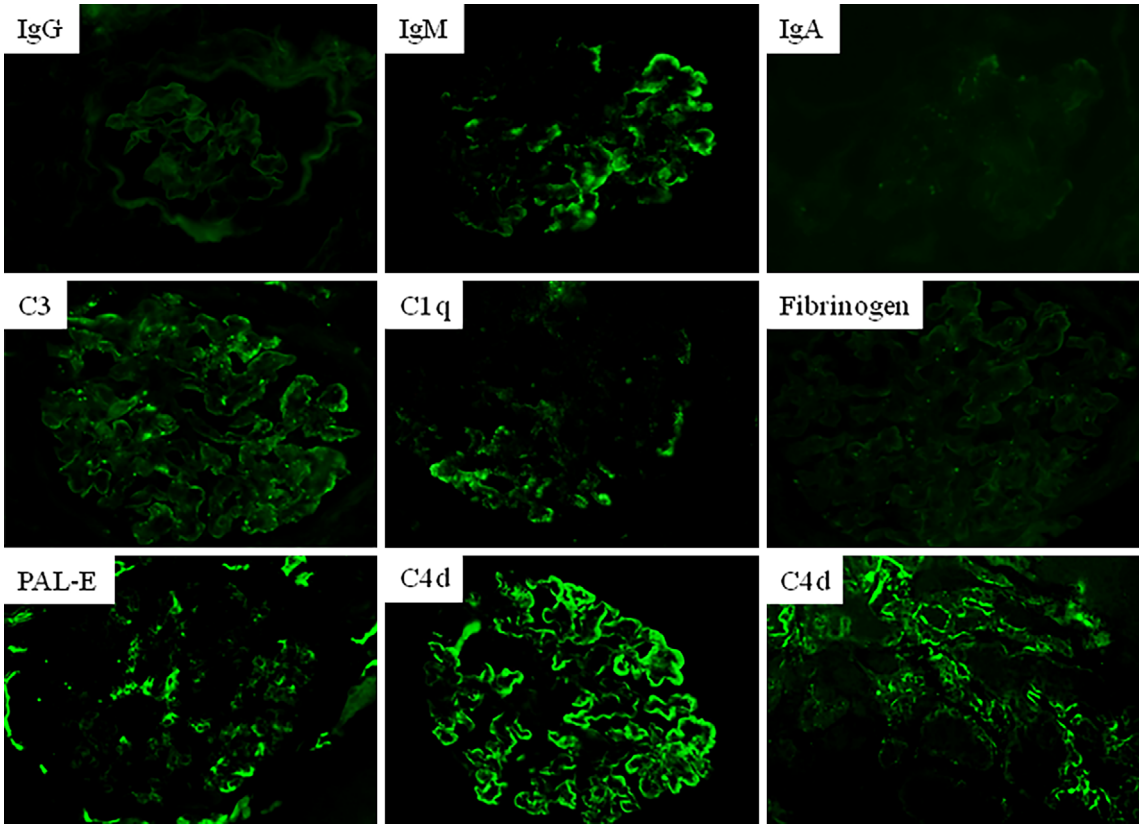

Figure 3. **Immunofluorescence findings. Focal and segmental irregular deposition of IgM, C3, and C1q was noted along the capillaries in the glomeruli. Pathologische Anatomie Leiden-endothelium (PAL-E) staining was positive along some glomerular capillaries. The deposition of C4d was evident on glomerular capillaries and on some peritubular capillaries.**

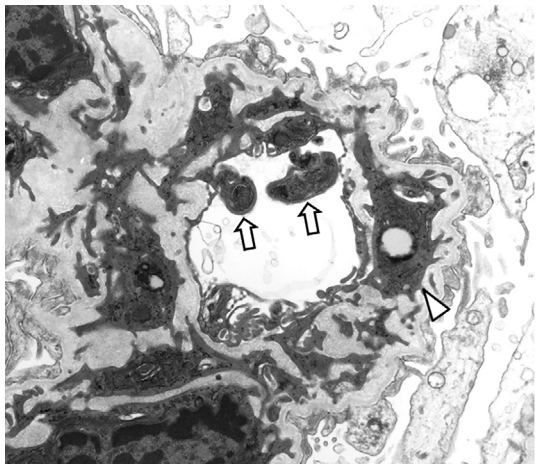

Figure 4. **Electron microscopy findings. Swelling and morphological changes in the endothelial cells of glomerular capillaries (arrows) and mesangial interposition into the subendothelial space were detected (arrowhead).**

noted along the glomerular capillaries (Fig. 3). Electron microscopy revealed swelling of endothelial cells in the glomerular capillaries, mesangial proliferation, and interposition into the subendothelial space (Fig. 4). Pathologische Anatomie Leiden-endothelium (PAL-E) staining indicated endothelial cell injury in the glomerular capillaries. Furthermore, the deposition of C4d was detected along the glomerular capillaries and partly on the peritubular capillaries (Fig. 3).

Discussion

Late-onset HSCT nephropathy in a narrow sense has been shown to be related to radiation, chronic GVHD, and long-term CyA treatments (4). In our case, C4d staining indicated that nephropathy was mainly caused by chronic GVHD. Furthermore, the only clinical manifestation associated with chronic GVHD observed was nephropathy; no extrarenal involvement developed clinically in our case.

Chronic GVHD is one of the most frequent complications of HSCT, and the target organs include the skin, nails, hair, mouth, eyes, genitalia, gastrointestinal tract, liver, lungs, musculoskeletal system, and hematopoietic immune system (5). Chronic GVHD may induce nephropathy, known as GVHD-related nephropathy. GVHD-related nephropathy presenting with nephrotic syndrome accompanied by other organ involvement has already been reported (6). However, to the best of our knowledge, there has been no report of chronic GVHD presenting with asymptomatic proteinuria and hematuria without other organ involvement, although it cannot be completely ruled out that other organ damage was clinically occult in consideration of the less severe symp-

toms of the present case than those previously reported.

GVHD-related nephropathy shows various histological patterns: (i) an immune complex deposition type such as membranous nephropathy, (ii) a podocyte injury type such as minimal change disease and focal segmental glomerulosclerosis, (iii) an endothelial injury type such as thrombotic microangiopathy (TMA), and (iv) a tubular injury type such as acute tubulointerstitial nephritis (7-10). In our case, PAL-E staining showed chronic glomerular endothelial cell injury (11). In addition, the deposition of C4d was diffusely detected on the glomerular capillaries and focally on peritubular capillaries. The deposition of C4d indicates complement activation on endothelial cells and antibody-mediated immune reactions to the targeted organ after transplantation (12). A recent study of a large series on TMA identified complement activation in the kidney as a common denominator of TMA in a heterogeneous group of patients, including HSCT-associated TMA (13). Mii et al. reported that the deposition of C4d in HSCT nephropathy indicates chronic antibody-mediated GVHD (10). Therefore, nephropathy in our case was considered to be affected by GVHD, despite the absence of the clinical extrarenal manifestations of GVHD. This was supported by the development of nephropathy during CyA tapering.

Radiation may induce nephropathy, known as radiation nephropathy, particularly when the radiation dose delivered is larger than 20 Gy (14). Radiation nephropathy shows swelling of glomerular capillary endothelial cells, double-contoured glomerular basement membrane, and an increased mesangial matrix in the glomeruli in addition to fibrinoid changes and intima expansion by the accumulation of mucoid-like materials in the arteries (15). These pathological findings were similarly observed in our case. We propose the following reasons for the potential effects of radiation on the histological changes observed in our case. Radiation tolerance varies due to many factors such as concomitant cytotoxic chemotherapy (16). Furthermore, tolerance of the renal parenchyma or renal artery to radiation is determined by the development of renal dysfunction or hypertension (17). Therefore, an even lower dose of radiation than the threshold generally considered to cause clinical complications may potentially induce histological changes without clinical symptoms. Therefore, it was not possible to completely exclude the effects of radiation in the development of HSCT nephropathy in our case.

CyA may also induce endothelial injury including vascular and glomerular lesions. In our case, asymptomatic proteinuria and glomerular hematuria appeared 4 months after the administration of CyA and persisted for 6 years after its withdrawal. CyA-induced endothelial injury may develop quickly over days to weeks following the initiation of CyA administration and is reversible with dose reductions (18). On the other hand, even a short-term administration and appropriate monitoring of CyA blood concentrations may induce endothelial injury (19). Therefore, it was not possible to completely exclude the adverse effects of CyA in our case.

Immunosuppressive therapies including steroids, CyA, cyclophosphamide, mycophenolate mofetil, and rituximab are recommended for GVHD-related nephropathy presenting with nephrotic syndrome (20, 21). Renin-angiotensin system inhibitors were previously found to be effective for radiation nephropathy (22). Our case presented without hypertension, nephrotic syndrome, or extrarenal GVHD manifestations. Furthermore, considering the deposition of C4d in the postulated stages of antibody-mediated rejection of kidney transplantation, our case was at stage 2, which represents accommodation (23). Therefore, the patient is currently under observation without medication.

In conclusion, we herein reported a case of HSCT nephropathy associated with chronic GVHD without obvious extrarenal involvement. The histological findings suggested antibody and/or complement activation in chronic GVHD as the cause of HSCT nephropathy in our case. Although typical GVHD-related nephropathy presents with clinical manifestations, it may also occur without any obvious extrarenal involvement.

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

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