

Renal Thrombotic Microangiopathy After Hematopoietic Stem Cell Transplantation: Involvement of Chronic Graft-Versus-Host Disease



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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a widely accepted treatment for malignant and nonmalignant disorders. Recent advances in transplantation techniques have increased the rate of long-term survival. However, kidney complications after HSCT are an important challenge.^{1,2} Recent studies have shown that the prevalence of chronic kidney disease (CKD) is approximately 20% in HSCT recipients.^{2–6} The existence of CKD can affect outcomes and reduce survival. In particular, among patients who developed end-stage renal disease (ESRD) and required dialysis, mortality rates were very high.⁵ It is important for nephrologists who treat transplant survivors to be aware of these complications so as to determine the optimal management of patients with CKD after HSCT.

Here, we report 4 cases of CKD after HSCT. All of them showed pathological renal thrombotic microangiopathy (TMA), and chronic graft-versus-host disease (GVHD) was clinically suspected as the cause of CKD. However, it is generally recognized that the kidney is rarely a target organ of GVHD.

CASE PRESENTATION

A clinical summary of our cases is shown in [Table 1](#) and [Figure 1](#). All patients underwent total body irradiation as a conditioning regimen and were administered calcineurin inhibitors (CNIs) for GVHD prophylaxis. Chimerism analysis of all our cases after HSCT detected more than 90% donor cells, and disease remission was sustained. Because of renal impairment and urinary abnormalities, renal biopsy

was performed. Histopathological findings of all cases showed a very similar pattern in the glomeruli and small arterioles. [Figure 2](#) shows representative images of case 3. Typical glomerular features were severe endothelial cell injury characterized by diffuse and globally enlarged subendothelial space, double contour of the glomerular basement membrane (GBM), mesangiolysis, and postmesangiolytic proliferative or postmesangiolytic sclerotic lesions. Global collapse of the glomerular capillaries and severe hyalinosis of the small arteries were occasionally seen ([Figure 2a](#) and [b](#)). Electron microscopy also showed persistent injury of the glomerular and peritubular capillaries (PTC) of the endothelial cells ([Figure 2c](#)). Furthermore, C4d deposition was evident in diffuse glomerular capillaries and was patchy on PTC ([Figure 2d](#)).

Case 1

A 49-year-old man presented with proteinuria and renal insufficiency. Renal biopsy was therefore performed. Two years previously, the patient had received an ABO-incompatible umbilical cord blood transplantation (UCBT). His course following UCBT was complicated by grade II acute and extensive chronic GVHD. He received low-dose tacrolimus for skin GVHD at that time. Renal biopsy results showed severe vascular endothelial cell injury. After the biopsy, we recommended a reduction in the tacrolimus dosage because we thought that the cause of endothelial cell injury was CNI nephrotoxicity. Unexpectedly, renal dysfunction became evident as the dosage of tacrolimus was decreased ([Figure 1a](#)). Renal impairment progressed when tacrolimus was stopped. Ultimately, the patient required dialysis.

Table 1. Clinical summary of cases presented

Characteristics	Case 1	Case 2	Case 3	Case 4
Age at biopsy, yr	49	42	40	28
Gender	Male	Male	Male	Male
Original disease	MDS	DLBCL	AA	AML
HSCT (age, yr)	UCBT (47)	UCBT (39)	Allogeneic BMT (39)	UCBT (27)
HLA	2 Mismatch	2 Mismatch	Full match	1 Mismatch
ABO incompatible	(+)	(+)	(-)	(+)
Conditioning regimen	CY+Flu	VP16+CY	CY+Flu+ATG	CY+Ara C
TBI	4 Gy	14 Gy	12Gy	12 Gy
GVHD prophylaxis	FK506	FK506	st MTX+CyA	FK506
Acute GVHD	(+) Grade II	(+) Grade III	(-)	(+) Grade I
Chronic GVHD	(+) skin, liver	(+) lung, brain	(-)	(-)
Reason for renal biopsy	Proteinuria, renal dysfunction	Renal dysfunction	Renal dysfunction	Renal dysfunction
Serum creatinine level (mg/dl)	2.44	2.12	1.82	2.84
eGFR (ml/min per 1.73 m ²)	24	30	35	24
Urinary protein level (g/gCre)	1.44	0.13	0.36	0.52
Pre HSCT renal dysfunction	(-)	(-)	(-)	(-)
Onset after HSCT	6 mo	3 yr	4 mo	5 mo
Clinical TMA	(-)	(+) Day 8	(-)	(+) Day 40
HT	(+)	(-)	(+)	(+)
DM	(-)	(+)	(-)	(-)

AA, aplastic anemia; AML, acute myelogenous leukemia; Ara-C, cytarabine; ATG, antithymocyte globulin; BMT, bone marrow transplantation; CY, cyclophosphamide; CyA, cyclosporin A; DLBCL, diffuse large B-cell lymphoma; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FK506, tacrolimus; Flu, fludarabine; HLA, human leukocyte antigen; HT, hypertension; MDS, myelodysplastic syndrome; st MTX, short-term methotrexate; TMA, thrombotic microangiopathy; UCBT, umbilical cord blood transplantation; VP16, etoposide.

Case 2

A 42-year-old man was referred to our department because of renal impairment. At the age of 39 years, UCBT was performed for the treatment of diffuse large B-cell lymphoma. Systemic transplantation-associated TMA (TA-TMA) with encephalopathy occurred promptly after transplantation. The blood concentration of tacrolimus for GVHD prophylaxis was 24.1 ng/ml at that time and continued at a high level (>20 ng/ml) for several days. Immediately stopping CNI improved clinical findings gradually. Complication due to grade III acute, and then extensive, chronic GVHD developed. Prednisolone was used mainly for GVHD treatment. When the dose of prednisolone was reduced, lung GVHD and brain GVHD occurred with progressive renal insufficiency (Figure 1b). However, an increased dose of prednisolone ameliorated physical findings and renal function. It seemed that renal insufficiency and the involvement of other organs were linked with each other. Therefore, long-term low-dose prednisolone was administered as a maintenance dose.

Case 3

A 40-year-old man was referred to our department because of renal insufficiency.

Two years previously, allogeneic bone marrow transplantation (BMT) was used to treat aplastic anemia. He did not develop acute or chronic GVHD; however, he did develop progressive renal insufficiency. When prednisolone and CNI for GVHD prophylaxis were discontinued, renal impairment became evident (Figure 1c). Based on the lessons learned from case 1, we first suspected chronic renal GVHD as the cause of renal insufficiency. Restarting low-dose prednisolone gradually ameliorated the patient's renal function.

Case 4

A 28-year-old man received an ABO-incompatible UCBT. Systemic TA-TMA-associated CNI toxicity occurred during an early phase after transplantation because the blood concentration of tacrolimus was very high. Acute kidney injury (AKI) developed afterward (Figure 1d). Temporary initiation of hemodialysis and discontinuation of CNI gradually improved the patient's physical findings and clinical parameters. However, mild renal dysfunction persisted after AKI. When prednisolone for GVHD treatment was decreased, renal impairment gradually progressed. When prednisolone was temporarily increased, a slight improvement in renal function was noted. However, the patient had a fungal infection, and prednisolone was tapered and stopped. Thereafter, his renal function gradually worsened.

DISCUSSION

In this case series, we have described 4 patients with chronic renal insufficiency after allogeneic HSCT. The pathological features of our cases were persistent microvascular endothelial injury in the glomeruli, PTC, and small arterioles of the kidney that were pathological renal TMA exactly. TA-TMA is a major complication after HSCT. It is assumed that TA-TMA resulting from microvascular endothelial injury is caused mainly by the use of CNIs and/or irradiation. When TA-TMA occurs, physicians commonly reduce or discontinue CNIs. Two of our case patients promptly developed TA-TMA associated CNI toxicity during an early phase after transplantation. Immediately stopping CNIs improved clinical findings. In contrast, late-onset chronic renal insufficiency was improved with the use of prednisolone despite severe renal endothelial injury on kidney biopsy. Changsirikulchai *et al.* reported an association between renal TMA and acute GVHD.⁷ They mentioned that stopping or decreasing the dose of CNI might not be helpful for managing TMA. Previously, we described cases of pathological renal TMA associated with chronic GVHD.^{8,9} We hypothesized that the renal vascular endothelium is a target of

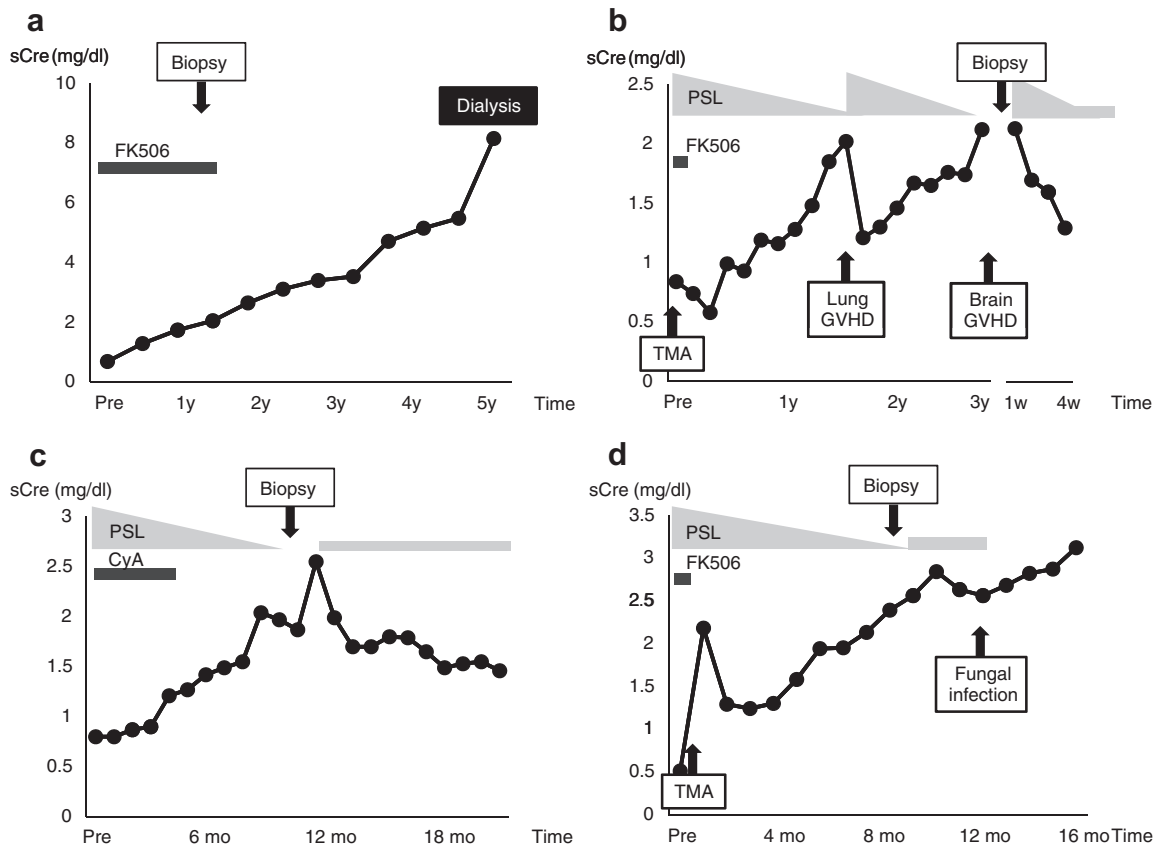


Figure 1. Time course of graft-versus-host disease (GVHD) treatment and serum creatinine level. (a) Case 1; (b) case 2; (c) case 3; (d) case 4. CyA, cyclosporin A; FK506, tacrolimus; PSL, prednisolone; sCr, serum creatinine; TMA, thrombotic microangiopathy.

GVHD. Furthermore, using a rat allogeneic BMT model, we determined that the kidney was a target organ of acute GVHD.¹⁰ Recently, Ishida *et al.* showed a renal-limited TMA case with urinary abnormality while reducing the CNI dosage after transplantation.¹¹ Renal biopsy results showed pathological renal TMA with C4d deposition in glomerular capillaries and patchy PTCs. These findings suggest that their case was affected by chronic renal GVHD. In our case series, the patient in case 3 clinically presented within renal-limited involvement and findings similar to that of the Ishida *et al.* case. However, their case differed from ours in that they did not attempt a treatment for renal-limited GVHD.

Regarding irradiation involvement, a recent study also suggested that the use of high-dose TBI was a risk factor for CKD.¹² All our cases received TBI. However, we considered that the exposure to TBI had a low potential for causing renal TMA, because administration of prednisolone ameliorated renal insufficiency in our case patients.

The typical target organs of GVHD include the gastrointestinal tract, liver, skin, eyes, and lungs.¹³ However, the kidney is considered an unlikely candidate for GVHD. Several cases of nephrotic syndrome have been reported as renal GVHD. Most of

these cases showed membranous nephropathy with subendothelial deposits on biopsy results.¹⁴ It has been suggested that the pathogenesis of membranous nephropathy is related to antigen–antibody complexes. In our cases, C4d deposition was observed on diffuse glomerular capillaries and was patchy on PTCs. C4d staining is a marker of classic complement activation and is a reliable marker of chronic humoral rejection in kidney transplantation.¹⁵ However, it is not an absolute marker because of the accommodation by the endothelial tissue that becomes resistant to the effects of the complement. Moreover, positive C4d staining for GBM alone has lower reliability due to the possibility of GBM remodeling.¹⁶ Hingorani *et al.* showed that urinary cytokines might be a useful marker of CKD after HSCT, especially for renal GVHD.¹⁷ They speculated that pro-inflammatory cytokines in the urine are a reflection of the inflammatory milieu of GVHD in the kidney. However, the relationship between kidney injury and GVHD remains controversial. Further studies involving more patients with CKD after HSCT are needed to clarify this relationship.

All our patients showed pathological renal TMA and were clinically suspected of having chronic GVHD. It has been indicated that renal vascular endothelium

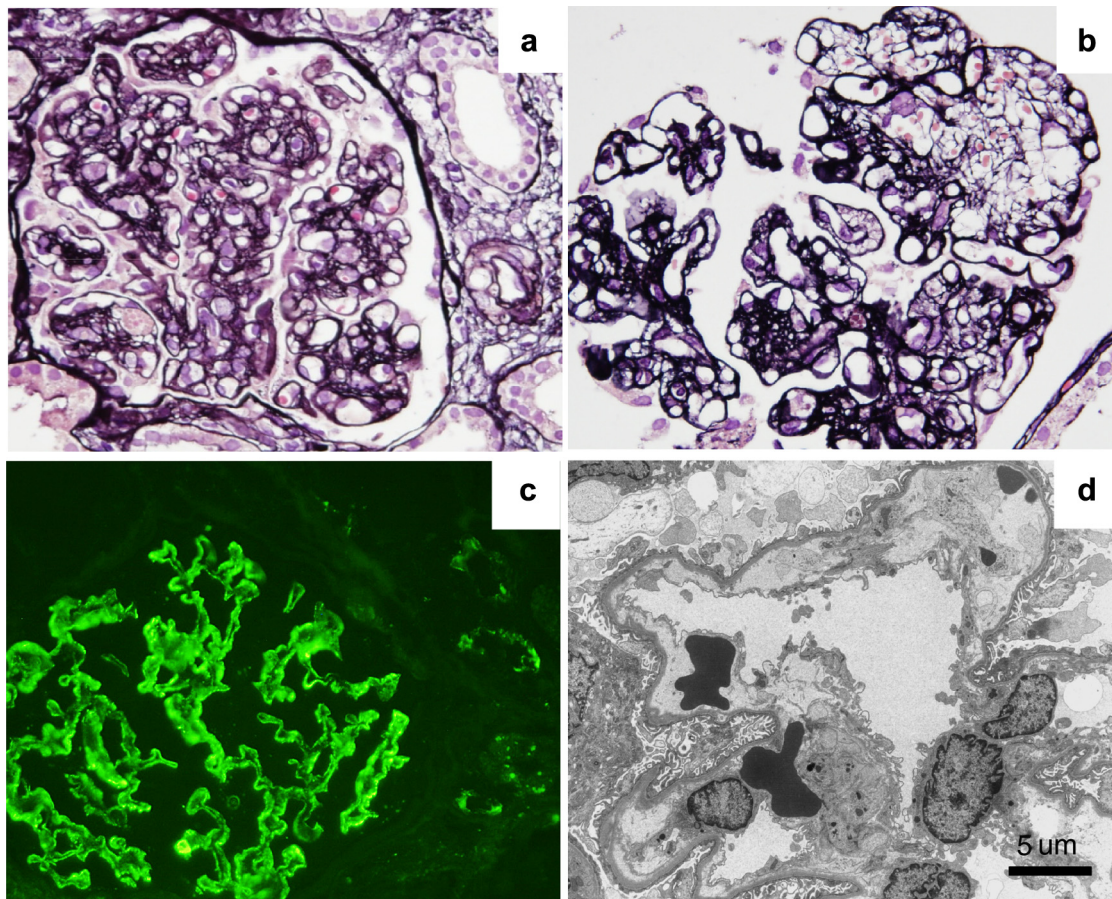


Figure 2. Kidney biopsy findings characterized by severe endothelial injury. (a) Periodic acid–silver methenamine (PAM) stain, original magnification $\times 400$; (b) PAM stain, original magnification $\times 600$; (c) C4d stain, original magnification $\times 400$; (d) electron microscopy, original magnification $\times 5000$. Histopathological findings of all cases showed a very similar pattern in the glomeruli and small arterioles. Representative images are presented (case 3). (a,b) Typical glomerular features were characterized by glomerular hypertrophy, a diffuse and globally enlarged subendothelial space, a double contour of the glomerular basement membrane, and mesangial proliferative, postmesangiolytic proliferative, or postmesangiolytic sclerotic lesions. (c) The diffuse and global pattern of C4d deposition was detected on the glomerular capillaries. Patchy staining for C4d was also evident in the peritubular capillaries. (d) Electron microscopy images showing persistent injury of the glomerular endothelial cells. Glomeruli showing double contour with enlarged subendothelial space and exudation of red blood cells into the expanded mesangial areas.

may be a target of GVHD. This means that renal GVHD leads to renal endothelial injury and TMA. Persistent renal vascular damage caused by renal GVHD contributes to the progression of CKD. When nephrologists encounter CKD after HSCT in patients with renal TMA, they should be aware of the possibility of GVHD and should consider an increased dose of immunosuppressive drugs.

DISCLOSURE

All the authors declared no competing interests.

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