De Novo Postallogeneic Hematopoietic Stem Cell Transplant Membranous Nephropathy

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Abstract

We report membranous nephropathy in a 61-year-old man after allogeneic hematopoietic stem cell transplant without chronic graft-versus-host disease. A diagnosis of acute myeloid leukemia was made, and the patient received hematopoietic stem cell transplants, twice, from different donors. The first donor was his brother and the second donor was an unrelated man.

Human leukocyte antigens between donors and recipient were fully matched. His clinical course was stable without acute or chronic graft-versus-host disease or relapse of acute myeloid leukemia with tacrolimus after the second hematopoietic stem cell transplant. Six months after the second hematopoietic stem cell transplant, tacrolimus was decreased gradually and discontinued because of tacrolimus-induced liver dysfunction. Three months after discontinuing the tacrolimus, the patient developed edema in his leg. The results of a blood analysis showed that plasma albumin level was 21 g/L and plasma total cholesterol level was 11.5 mmol/L, while results from a urinalysis showed proteinuria of 5.6 g/d without hematuria. No abnormalities in the skin, mucosal tissues, and other organs suggestive of chronic graft-versus-host disease were seen. A renal biopsy was done to investigate the cause, which revealed renal disease. Electron microscopic analysis showed dense deposits in the subepithelial region in all glomeruli. Immunofluorescence analysis showed the deposition of IgG4 and C3c in the subepithelial space of all glomeruli. Membranous nephropathy was diagnosed. He then was administered prednisolone at a dosage of 45 mg/d (0.7 mg/kg/d). After prednisolone treatment, urine protein and hypoalbuminemia were markedly improved, and his leg edema disappeared.

These results suggest that this membranous nephropathy may have been de novo membranous nephropathy after hematopoietic stem cell transplant because it developed after hematopoietic stem cell transplants without chronic graft-versus-host disease.

Key words: *Membranous nephropathy, Allogeneic hematopoietic stem cell transplantation, Chronic graft-versus-host disease*

Introduction

Chronic graft-versus-host disease (GVHD) develops after the first 100 days after an allogeneic hematopoietic stem cell transplant, presenting with several manifestations mimicking autoimmune disease involving organs such as the skin, eyes, mouth, liver, respiratory tract, and the immune system.[1,2] Nephrotic syndrome after hematopoietic stem cell transplant is rare. Nephrotic syndrome after hematopoietic stem cell transplant is mainly related to membranous nephropathy, and less frequently to minimal change disease, diffuse proliferative glomerulonephritis, or focal segmental glomerular nephritis.[3,4] Although the mechanism of the nephrotic syndrome after hematopoietic stem cell transplant has not been elucidated, it is associated with ceasing immunosuppressive agents and chronic

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GVHD.[5-7] However, there is debate over the entity of de novo nephrotic syndrome after hematopoietic stem cell transplant without chronic GVHD.[3,8] We report a case of de novo membranous nephropathy after hematopoietic stem cell transplant without chronic GVHD.

Case Report

A 61-year-old man presented to us with a low-grade fever in May 2007. Results of a blood analysis showed marked leukocytosis and bone marrow examination revealed acute myeloid leukemia in June 2007. He received a hematopoietic stem cell transplant in January 2008. The donor was his brother and HLA antigens (A, B, C, DR, DQ, DR) of the donor and the recipient were fully matched.

Meanwhile, his clinical course was stable with cyclosporin; however, his leukemia relapsed in August 2009. Therefore, he received hematopoietic stem cell transplant again in March 2010. The donor was an unrelated man and all HLA antigens of donor and recipient were fully matched. Chimerism short tandem repeat examinations of bone marrow after second hematopoietic stem cell transplant showed few recipient-derived hematopoietic cells (< 5%) in March 2010. After that, he was orally administered tacrolimus to prevent acute and chronic GVHD; however, the dosage was reduced and discontinued in September 2010 because of adverse effects (eg, liver dysfunction). After ceasing tacrolimus, his liver dysfunction improved.

Subsequently, the patient developed leg edema and in January 2011, proteinuria was detected. He was admitted to Jichi Medical University hospital in March 2011. On examination, he had periorbital and leg edema. No abnormalities were observed in the skin, mucosal tissues, or other organs suggestive of chronic GVHD. His blood pressure was 129/72 mm Hg. The results of a blood analysis showed that his plasma albumin level was 21 g/L and plasma total cholesterol level was 11.5 mmol/L. The results of a urinalysis showed proteinuria of 5.6 g/d without hematuria (Table 1). A diagnosis of nephrotic syndrome was made. A renal biopsy was done to investigate the cause. Although the renal biopsy specimen did not show global sclerosis, crescent formation, mesangial cell proliferation, and mesangial matrix incretion by light microscopy—an electron microscope analysis showed dense deposits in the subepithelial region and material extensive global effacement of the visceral epithelial foot processes (Figure 1A, B).

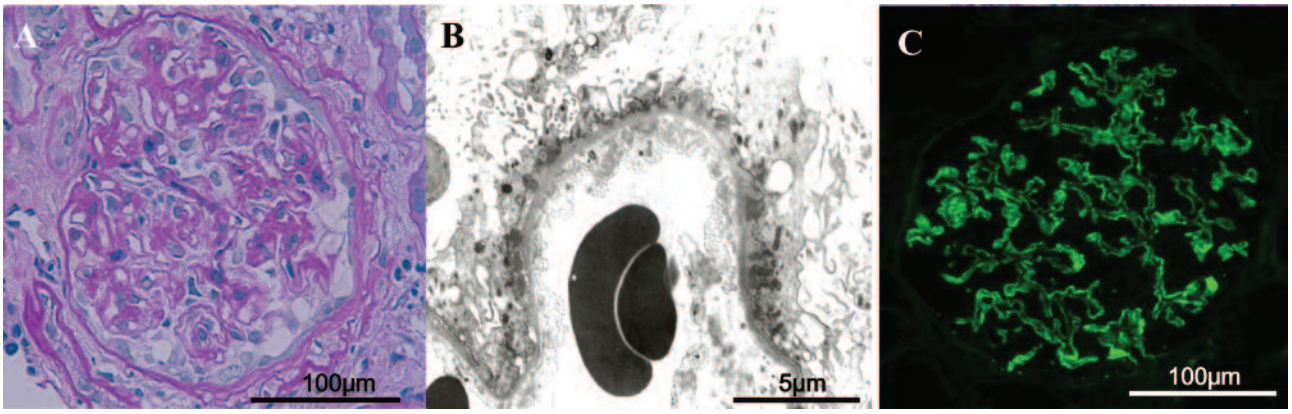
An immunofluorescent analysis showed fine granular deposition of IgG and C3c in the subepithelial space of all glomeruli (Figure 1C). The IgG subclass analysis was positive for IgG4 and negative for IgG1, IgG2, and IgG3 among the IgG. We diagnosed the patient's nephrotic syndrome as membranous nephropathy stage II. He was administered prednisolone at a dosage of 45 mg/d (0.7 mg/kg/d) to treat the membranous nephropathy. After prednisolone treatment, urine protein and hypoalbuminemia markedly improved

Table 1. Laboratory Findings on Admission

Blood Analysis				Urinary Analysis	
WBC	6800 × 10^9/L	AST	26 U/L	Volume	1700 mL/d
RBC	432 × 10^{12}/L	ALT	25 U/L	Protein	5.6 g/d
Hb	11.2 g/dL	LDH	179 U/L	Na	160 mmol/d
Ht	0.43	ALP	276 U/L	K	44.2 mmol/d
Plt	22.2 × 10^9/L	CPK	84 U/L	Cr	1.21 g/d
TP	52 g/L	γ-GTP	194 U/L		
Alb	21 g/L	IgG	8.2 g/L	RBC	5-6 /field
BUN	7.5 mmol/L	IgA	1.7 g/L	WBC	3-4 /field
Cr	75.5 μmol/L	IgM	0.8 g/L	NAG	25.8 U/L
Na	140 mmol/L	C3	1.4 g/L	$ß_2$ microglobulin	3.7×10^{-4} g/L
K	4.4 mmol/L	C4	0.3 g/L	Ccr	1.49 mL/s
Cl	8.7 mmol/L	ANA	(-)		
T-chol	11.5 mmol/L				
TG	1.8 mmol/L				
CRP	1.0 mg/L				

Abbreviations: Alb, albumin; ALP, alcaline phosphatase; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ccr, creatinine clearance; Cl, chloride; CPK, creatine phosphokinase; Cr, creatinine; CRP, C-reactive protein; Hb, hemoglobin; Ht, hematocrit; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; K, potassium; LDH, lactate dehydrogenase; Na, sodium; NAG, N-acetyl-β-D-glucosaminidase; Plt, platelets; RBC, red blood cells; T-chol, total cholesterol; TG, triglyceride; TP, total protein; WBC, white blood cells; γ-GTP, γ-glutamyl transpeptidase

Figure 1. Histopathologic Features of Membranous Glomerulonephritis



(A) Light microscopy, Periodic acid-Schiff (PAS) staining: normal aspect of glomeruli. **(B)** Electron microscopy: global subepithelial electron-dense deposition, and material extensive global effacement of visceral epithelial foot processes. **(C)** Immunofluorescence study using a specific anti-IgG antibody: Presence of marked granular subepithelial deposits.

within 1 month, and face and leg edema disappeared.

Discussion

We describe a case of membranous nephropathy after hematopoietic stem cell transplant without chronic GVHD. Although membranous nephropathy has been reported as the most-common nephrotic syndrome after hematopoietic stem cell transplant, chronic GVHD was present in 88% of cases of membranous nephropathy after hematopoietic stem cell transplant.[5] Although the mechanism of membranous nephropathy after hematopoietic stem cell transplant associated with chronic GVHD has not been elucidated, immune conflict between donor lymphocyte and recipient tissues is considered a contributing factor. Chronic GVHD mimics or is associated with various autoimmune diseases (eg, systemic sclerosis, Sjögren syndrome, myasthenia gravis, and polymyositis).[9-11] Membranous nephropathy may represent another consequence of this graft-host conflict.[4]

On the other hand, there are several case reports of membranous nephropathy after hematopoietic stem cell transplant without chronic GVHD; these suggest the existence of de novo membranous nephropathy after hematopoietic stem cell transplant.[3,8] The suggested mechanism of de novo membranous nephropathy after hematopoietic stem cell transplant is as follows: Donor-derived chimeric mesangial cells,[12] tubular cells,[13] and endothelial cells[14] have been detected in renal biopsies performed in patients who have undergone hematopoietic stem cell transplant. Donor-derived hematopoietic-origin podocytes also have been suggested.[15] These intraglomerular chimeric cells may trigger a host-graft reaction leading to membranous nephropathy.[3]

Because sex and human leukocyte antigens were matched between the first and second donors and the recipient in the present case, we were unable to determine chimeric cells in kidney biopsy specimen. In the present case, IgG4 was positively stained, and IgG1, IgG2, and IgG3 did not stain in the subepithelial space of glomeruli. These features are similar to idiopathic membranous nephropathy.[16] It has been reported that IgG1 and IgG4 are the predominant types of IgG in idiopathic membranous nephropathy[16]; however, all IgG subclasses are present in lupus-associated membranous nephropathy,[16] and IgG1 and IgG2 predominate in malignancy-associated membranous nephropathy.[17]

Our patient developed membranous nephropathy after withdrawing tacrolimus. This withdrawal of immunosuppression also may contribute to host-graft reaction in the kidneys leading to membranous nephropathy. Further studies are required to confirm the existence and identify the mechanisms of de novo membranous nephropathy after hematopoietic stem cell transplant. Treatment of membranous nephropathy after hematopoietic stem cell transplant mainly involves prednisolone and other immunosuppressives (eg, cyclosporine and cyclophosphamide). Because it was reported that intense immunosuppression after hematopoietic stem cell transplant can cause recurrence of acute myeloid

leukemia,[18] we selected a prednisolone monotherapy. After prednisolone treatment, membranous nephropathy improved without relapse of acute myeloid leukemia.

Experimental data and clinical observations suggest a case of de novo membranous nephropathy after HSP hematopoietic stem cell transplants. The appropriate degree of clinical suspicion and observation, accompanied by renal biopsy, is required to diagnose and treat de novo membranous nephropathy after HSP hematopoietic stem cell transplants.

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