

# Nephrotic Syndrome after Hematopoietic Cell Transplantation: Do Glomerular Lesions Represent Renal Graft-versus-Host Disease?

Kirsten Brukamp,\* Alden M. Doyle,\* Roy D. Bloom,\* Nancy Bunin,<sup>†</sup> John E. Tomaszewski,<sup>‡</sup> and Borut Čižman\*

\*Renal-Electrolyte and Hypertension Division, Department of Medicine, <sup>†</sup>Division of Oncology, The Children's Hospital of Philadelphia, and <sup>‡</sup>Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Glomerular disease associated with nephrotic syndrome has rarely been recognized as a distinct complication of allogeneic hematopoietic cell transplantation. Case reports in the English and Japanese literature since 1988 have described variable glomerular histology, comprising mainly membranous glomerulonephritis (MGN) in almost two thirds and minimal change disease (MCD) in nearly one quarter of patients. Review of the literature reveals a close temporal relationship between the development of nephrotic syndrome shortly after cessation of immunosuppression and the diagnosis of chronic graft-versus-host disease (GVHD). An association of glomerular disease with simultaneous GVHD was seen in 47% of patients overall. Nephrotic syndrome followed GVHD within 5 months in 60% of the combined MCD and MGN reports. A decrease in immunosuppressive medication use was linked to nephrotic syndrome occurrence within 9 months in 63% of patients with MCD and MGN. MCD occurred earlier after hematopoietic cell transplantation, was diagnosed sooner after medication change, and exhibited a better prognosis in comparison with MGN. Glomerular lesions after hematopoietic cell transplantation may therefore represent the renal manifestation of GVHD. Further studies are warranted to delineate the pathogenesis of this complication.

*Clin J Am Soc Nephrol* 1: 685–694, 2006. doi: 10.2215/CJN.00380705

The emergence of hematopoietic cell transplantation (HCT) for malignant and particularly so-called benign hematopoietic indications has resulted in the increasing recognition of acute and chronic renal failure as a complication. In close temporal proximity to the HCT, well-described conditions such as medication-induced nephrotoxicity, tumor-lysis syndrome, septic-ischemic tubular necrosis, and drug- or virus-induced hemorrhagic cystitis may occur (1). Delayed decline of kidney function is usually caused by radiation nephropathy, calcineurin inhibitor nephrotoxicity as a result of graft-versus-host disease (GVHD) prophylaxis, and hemolytic-uremic syndrome (1). The term *bone marrow transplant nephropathy* (2,3) has thus far been used to refer to late renal complications after HCT reminiscent of hemolytic-uremic syndrome, attributed to total body irradiation and nephrotoxic therapies. This lesion is characterized by mesangiolytic, mesangial matrix expansion, glomerular capillary widening, endothelial injury and dropout, and subendothelial space widening secondary to deposition of fibrin and newly formed basement membrane (2,3).

GVHD is a serious complication of allogeneic HCT, which can affect skin, eyes, mouth, serous membranes, liver, gastrointestinal and respiratory tracts, and the musculoskeletal, hematopoietic, and immune systems. Acute GVHD (4), affecting up to 80% of patients, usually occurs within days to 2 mo after the transplantation and typically involves the immune system, skin, liver, and gastrointestinal tract. The pathophysiology is complex and consists of cytokine activation of antigen-presenting cells after radio-chemotherapy, which leads to T cell proliferation and differentiation into effector cells. These cells secrete cytokines that mediate apoptosis, tissue injury, and a positive inflammatory feedback loop (5). Chronic GVHD (6), by definition, appears >100 d after transplantation. Risk factors for chronic GVHD include history of moderate to severe acute GVHD, older age, extensive skin involvement, and thrombocytopenia.

Despite increasing knowledge about GVHD, nephrotic syndrome (NS) has not been studied extensively, albeit systematically, in this context. Case reports describe various pathologic glomerular changes after HCT. Herein, we report two typical cases followed at our institution, as well as two patients with less frequent features, and we review previous case reports to identify common characteristics among patients.

Published online ahead of print. Publication date available at [www.cjasn.org](http://www.cjasn.org).

**Address correspondence to:** Drs. Kirsten Brukamp and Borut Čižman, Renal-Electrolyte and Hypertension Division, Department of Medicine, University of Pennsylvania School of Medicine, 700 Clinical Research Building, 415 Curie Boulevard, Philadelphia, PA 19104. Phone: 215-573-1830; Fax: 215-898-0189; E-mail: [brukampk@uphs.upenn.edu](mailto:brukampk@uphs.upenn.edu), [bcizman@ceeb.med.upenn.edu](mailto:bcizman@ceeb.med.upenn.edu)

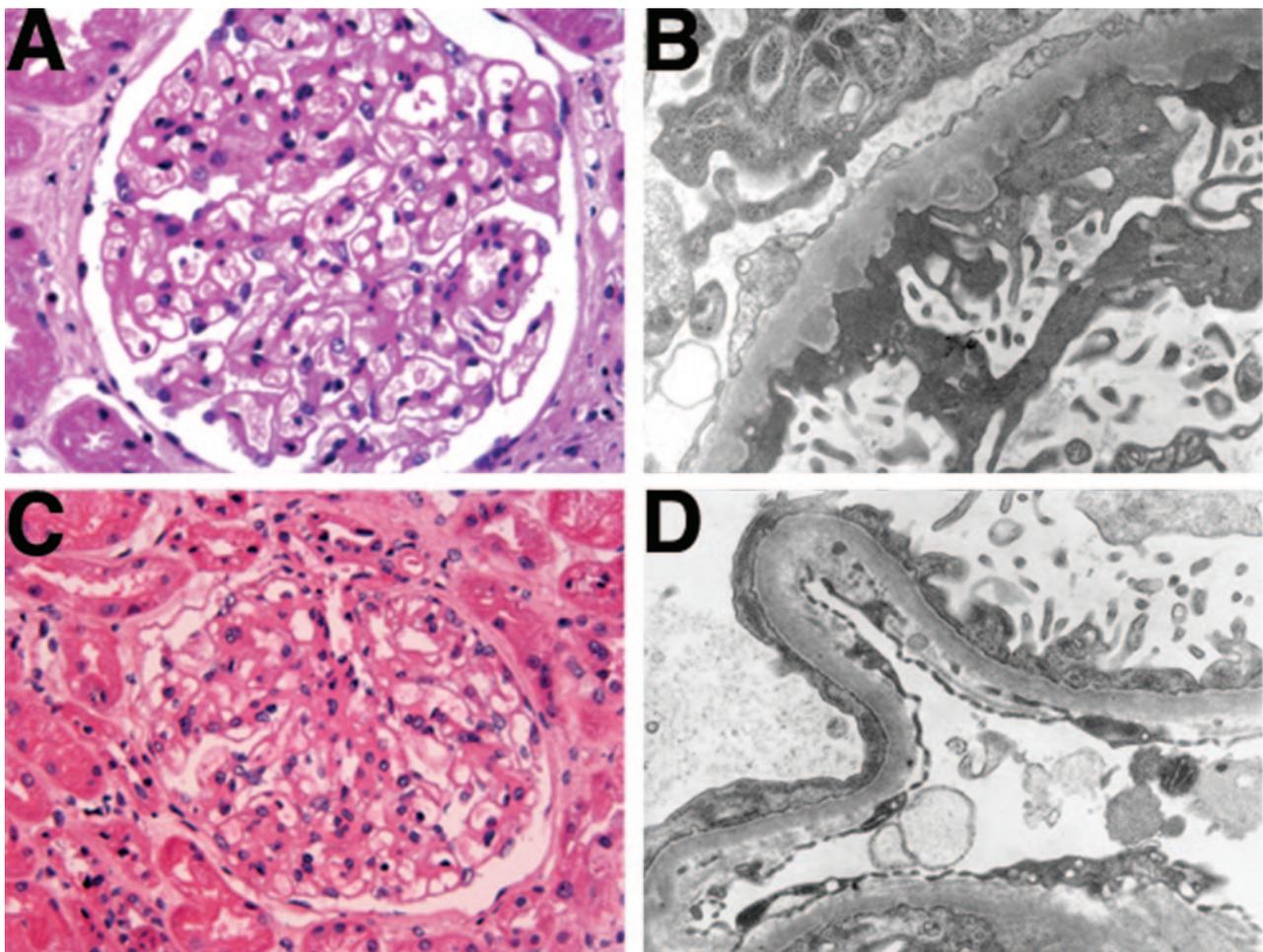
## Typical Case Reports

A white man (patient 1), born in 1957, underwent an allogeneic peripheral blood progenitor cell transplantation (PBT) af-

ter cyclophosphamide and busulfan conditioning therapy from his HLA-identical brother at the Hospital of the University of Pennsylvania (HUP) in September 2001 for first acute myelogenous leukemia (AML M2) relapse. His course was complicated by development of acute skin GVHD despite cyclosporine A (CsA) prophylaxis as well as chronic lung GVHD, consisting of changes reminiscent of bronchiolitis obliterans organizing pneumonia and pleural effusions, in March 2002. The patient was treated with prednisone and CsA, which were tapered and discontinued in February 2003. In July 2003, the patient was found to have new, biopsy-proven chronic GVHD with skin, lung, and pericardial involvement. At the same time, the patient was also noted to have NS, characterized by anasarca, hypoalbuminemia (1.9 mg/dl), proteinuria (22 g/d), hypercholesterolemia (340 mg/dl), and hematuria (5 red blood cells per high-power field on urinalysis). Hepatitis B and C serologies and antinuclear antibody (ANA) titers were within normal

limits. The patient began to take prednisone 20 mg/d along with a loop diuretic and an angiotensin II receptor blocker. A kidney biopsy specimen obtained in October 2003 revealed findings of early membranous glomerulonephritis (MGN; Figure 1, A and B). Secondary to steroid resistance, tacrolimus and mycophenolate mofetil were added in November 2003. His edema resolved, and his proteinuria decreased to <0.3 g/d. His creatinine remained relatively stable at 0.9 to 1.2 mg/dl.

A white man (patient 2), born in 1972, received an allogeneic PBT from his HLA-identical brother at HUP in January 2003 after conditioning therapy with cyclophosphamide and fludarabine. His nodular-sclerosing Hodgkin's lymphoma (HL), stage III B at diagnosis in August 2000, had relapsed despite several cycles of chemotherapy regimens, radiation, and an autologous progenitor cell transplantation in January 2002. After the allogeneic HCT in January 2003, the patient was in complete clinical remission from HL. The patient was admitted



**Figure 1.** Glomerular lesions in patients after hematopoietic cell transplantation. (A and B) Patient 1: Early membranous glomerulonephritis. No definitive basement membrane spikes were present on histology (A), but the electron microscopy (B) showed epimembranous immune complex deposition. The immunofluorescence (not shown) confirmed granular immune deposition for IgG along the capillary loops. In addition, occasional mesangial and subendothelial deposits and rare focal segmental glomerulosclerosis were also noted (not shown). (C and D) Patient 2: Mild mesangial proliferative glomerulopathy. Histology (C) showed very mild mesangial proliferation. Mild interstitial chronicity was also present (not shown). Immunofluorescence (not shown) was negative. Electron microscopy (D) revealed diffuse effacement of the visceral epithelial foot processes, involving approximately 90% of the glomerular capillary loops.

to HUP in July 2003 with dyspnea on exertion, foamy urine, facial edema, and a rash on his face and on both arms for 1 wk. His medications had included CsA for GVHD prophylaxis until 1 mo before presentation. He was found to have NS with anasarca, hypoalbuminemia (albumin 1.5 g/dl), microscopic hematuria, and proteinuria of 23.3 g/d, as well as acute renal failure (creatinine 2.4 mg/dl, increased from the previous value of 1.4 mg/dl in the same month). Tests such as hepatitis B and C serologies, complement C3 and C4 levels, ANA, ANCA, serum and urine protein electrophoresis, and antistreptolysin titer were within normal limits, and blood cultures were negative. A kidney biopsy revealed rare mesangial proliferative glomerulonephritis (Figure 1, C and D). A skin punch biopsy of the arm showed new chronic GVHD. The patient responded promptly to diuretic therapy and prednisone treatment, beginning at 1 mg/kg per d. At 4 wk, the forearm skin lesions had disappeared, and only trace lower leg edema was present (creatinine 1.2 mg/dl). Prednisone was tapered, but in April 2004, the patient had a relapse of NS with peripheral edema, nephrotic-range proteinuria, and hypoalbuminemia. His prednisone dose was increased again to 1 mg/kg per d with excellent response, followed by a taper to 10 mg/d in July 2004. In August 2004, a chest computed tomography scan revealed new lymphadenopathy indicating possible recurrence of HL, and the patient is currently receiving chemotherapy. No recurrence of NS or chronic kidney disease (CKD) progression has been noted.

## Discussion

In patient 1, the NS appearance in July 2003 coincided with GVHD involvement of a new organ as well as worsening in previously affected organs after discontinuation of CsA and prednisone in February 2003. This temporal relationship is suggestive of NS's being a manifestation of GVHD.

The mesangial proliferative glomerulopathy (Figure 1C) seen in patient 2 was characterized by extensive foot process effacement (Figure 1D) and mild interstitial chronicity. This interstitial chronicity precluded the histopathologic diagnosis of classic minimal change disease (MCD). However, nephrotoxic insults surrounding the HCT and the use of CsA as GVHD prophylaxis may have resulted in chronic interstitial atrophy, which led to the patient's preexisting stable CKD stage 2. The mesangial proliferative glomerulonephritis may then have been the sole acute histologic correlation of NS, thereby constituting an MCD variant. The patient's responsiveness to glucocorticosteroid therapy thus far supports the latter claim.

The differential diagnosis of NS in a patient with a history of HL includes MCD as a manifestation of lymphoma recurrence (7,8). The association is rare, and the pathophysiology is unknown. A delay of up to 19 mo has been described, in one case report (9), between onset of NS, which spontaneously remitted, and diagnosis of recurrent HL. However, the glomerulopathy typically occurs within 6 mo before a diagnosis of recurrent HL is made. In our case, the patient was in complete remission after HCT for 19 mo, and therefore 13 mo after first development of NS. Although a minimal possibility remains that the NS occurrence was related to the HL relapse, the close proximity be-

tween the cessation of CsA prophylaxis and the development of new skin GVHD along with NS 2 to 3 wk later is highly suggestive of a causal association. NS in this patient is more likely a manifestation of GVHD rather than a prodrome of HL recurrence. To our knowledge, this case constitutes the first description of NS after HCT for HL.

In addition to patients 1 and 2, we noted two patients in our institution without clear-cut relationships between the NS presentation and HCT, chronic GVHD, or medication change. Although these cases do not illustrate supposedly typical relationships, their inclusion within the scope of a descriptive analysis is warranted as they demonstrate NS occurrences after HCT. Otherwise, bias would be introduced by overestimation of tight links between NS and potentially inciting events. It is conceivable that some cases do not exhibit possibly typical risk factors before NS presentation despite a connection to HCT, probably dependent on the underlying histologic correlate and its progression pattern. Both additional patients received a diagnosis of focal segmental glomerulosclerosis (FSGS), which may be either a diagnosis that is linked directly to the HCT or a secondary phenomenon after a different glomerular insult.

A white man of Italian ancestry, born in 1956, received a diagnosis of chronic myelogenous leukemia (CML) in March 1993, for which he received an allogeneic bone marrow transplantation (BMT) from his HLA-identical sister in March 1993, followed by acute skin GVHD. He presented with nephrotic-range proteinuria in May 1998 (creatinine 2.0 mg/dl; proteinuria 4.1 g/d; perinuclear ANCA, cytoplasmic ANCA, and complement levels C3 and C4 unremarkable), when his kidneys were borderline small with mildly increased echogenicity. A renal biopsy revealed global glomerulosclerosis in 13 of 15 glomeruli, while one of the two remaining glomeruli had a small segmental area of sclerosis. Electron microscopy showed focal areas of podocyte foot process effacement, and moderate fibrosis and tubular atrophy were seen in the interstitium. Currently, the patient has CKD stage 4, and he may receive a preemptive living-related donor kidney transplantation from his bone marrow donor in the future (10).

A female patient, born in 1979, underwent an allogeneic BMT from her HLA-identical sister for sickle cell  $\beta$  thalassemia at the Children's Hospital of Philadelphia in November 1995 after conditioning with cyclophosphamide, busulfan, and antithymocyte globulin, complicated by acute skin GVHD. In November 1997, she developed facial swelling and pedal edema, and laboratory tests were consistent with nephrotic syndrome (creatinine 0.8 mg/dl; proteinuria 3.8 g/d; complement C3 135 mg/dl; ANA and antibodies for hepatitis B and C negative). A renal biopsy in December 1997 showed global sclerosis in two of 20 glomeruli, whereas others had varying degrees of hypercellularity with increased mesangial cells and diffuse foot process effacement. The patient received an intravenous methylprednisolone pulse therapy and oral prednisone thereafter without significant improvement. A second renal biopsy, performed in January 2000 to assess chronicity, prognosis, and future treatment after 2 yr of glucocorticosteroid therapy, was consistent with fully developed FSGS (global sclerosis in seven of 15 glomeruli, variable degrees of segmental sclerosis in the

remaining glomeruli, focal visceral epithelial foot process effacement, moderately fibrotic interstitium, and tubular atrophy). Prednisone was then stopped, and the patient's CKD progressed on an angiotensin-converting enzyme inhibitor. Ultimately, the patient may be a candidate for renal transplantation from her original bone marrow donor (10).

## Analysis of the Literature and Discussion

A literature search was conducted to place individual cases into perspective and to identify global characteristics of NS occurrence after HCT. Case reports were identified by PubMed search (with combinations of terms such as "nephrotic syndrome," "glomerular disease," "hematopoietic cell transplantation," and "graft-versus-host disease") and by following references in the identified articles. Main case features were abstracted, and statistical analysis was performed with SPSS 13.0 (SPSS Inc., Chicago, IL). Time values that were ambiguous in the literature were rounded up to the next month, and concurrent values and those that were <1 mo were considered as 0 and 1 mo, respectively, for statistical purposes, to bias in favor of underestimating an effect. Percentages were calculated under exclusion of cases for which values were not reported, except where otherwise noted, as the number of missing values was usually low.  $P < 0.05$  was considered statistically significant for analysis with the nonparametric Mann-Whitney  $U$  test and the nonparametric Spearman  $\rho$  correlation test.

Forty-two previous, well-documented cases (11–43) that link allogeneic HCT and glomerular kidney disease have been published between 1988 and 2005. The pertinent patient characteristics of MGN and MCD cases, which are relevant for the discussion, are summarized in Table 1. Main individual findings of the reviewed 46 cases are listed in complementary Table 2. Other publications (44,45) refer to additional cases, but the details are too scarce to take these patients into account for detailed analysis in this review. In an additional case, NS developed after bone marrow nephropathy was found on renal

histology, but the patient did not undergo biopsy again (46). A cohort study (43) of nonmyeloablative HCT listed seven patients with NS, three of whom did not receive a histologic diagnosis and therefore were not included. Two patients with a nephritic pattern as a result of ANCA-associated glomerulonephritis after autologous (47) and allogeneic (48) HCT were also excluded, and two pediatric case reports of membranoproliferative glomerulonephritis after autologous HCT (49) and of glomerular vasculopathy, resembling thrombotic microangiopathy, after cord blood transplantation (50) seemed unrelated as well.

A total of 61% of the patients carry a diagnosis of MGN, and MCD affects 22% of patients. This approximate 3:1 ratio could possibly be due to publication bias, as MGN is favored in most early case reports. Mesangial proliferative glomerulonephritis may be interpreted as an MCD variant (27; our study). Other diagnoses vary and include FSGS that may be secondary to other types of glomerular lesions, mesangial IgA deposition with crescent formation, and diffuse proliferative and crescentic glomerulonephritis that may be superimposed on a different glomerular disease.

Histopathologic findings, both for glomerular disease and for extraglomerular changes, are not straightforward in some studies. For example, in two cases here classified only descriptively as immune complex-mediated glomerulonephritis, the authors reported glomerular subendothelial and subepithelial electron-dense deposits despite negative immunofluorescence, without arriving at a distinct diagnosis (12). FSGS features can accompany and follow a diagnosis of both MGN (17) and MCD (21). Several histopathologic specimens (12,13,25,28–30,32,42) exhibit interstitial infiltrates of variable intensity, consisting of lymphocytes, monocytes, or macrophages. Two studies (30,42) confirm a donor origin of mononuclear interstitial infiltrates. Rare findings include immune complex deposition in the tubular basement membrane along with a diagnosis of MGN (23).

The predominant underlying hematologic diagnosis is CML; acute myeloblastic leukemia and aplastic anemia are other common diagnoses. A shift from BMT toward PBT can be seen in the MGN and MCD groups of renal pathology over time (data not shown), a phenomenon that likely reflects the change of clinical practice in HCT. A comparison between the half of cases published first (11–31) with the more recent half (32–43; our study) reveals a parallel distribution of pathology (13 *versus* 15 MGN, 5 *versus* 5 MCD, and 5 *versus* 3 miscellaneous cases in each group) with a reversal of BMT and PBT frequency (71% BMT in the earlier half and 75% PBT in the later half). This finding suggests a lack of pathophysiologic impact of HCT modality on MGN *versus* MCD occurrence. It should be noted that a recent meta-analysis (51) has confirmed individual study results that chronic GVHD is more likely after PBT than after BMT, which may be explained by the transfer of a greater T cell dose. The question of whether the continuing relative increase of PBT among HCT leads to a greater probability of NS as a complication is beyond the scope of this review because of the lack of an adequate epidemiologic approach with higher patient numbers.

The vast majority of patients have evidence of acute and

Table 1. Comparative summary of patients with NS and associated MGN and MCD after allogeneic HCT<sup>a</sup>

Variable	MGN	MCD
Proportion of all cases (%)	61	22
Male patients (%)	75	40
History of acute GVHD (%)	78	40
Occurrence of chronic GVHD (%)	88	50
HCT to chronic GVHD (mo)	6 (8.5 ± 5.6)	9 (9 ± 4.1)
Age at NS onset (yr)	41 (37 ± 15)	31 (30 ± 16)
Creatinine at NS onset (mg/dl)	0.9 (1.0 ± 0.7)	1.2 (1.4 ± 0.7)
Proteinuria at NS onset (g/d)	7.6 (12 ± 9)	13 (13 ± 7)
HCT to NS onset (mo)	14 (16 ± 7)	8 (12 ± 10) <sup>b</sup>
Concomitant GVHD and NS (%)	52	30
GVHD to NS onset (mo)	0 (5.0 ± 7.0)	2 (5.9 ± 9.3)
Medication change to NS onset (mo)	5 (3.9 ± 2.7)	1 (1.1 ± 0.4) <sup>b</sup>
Complete remission (%)	27	90

<sup>a</sup>Values are reported as percentages or as median (mean ± SD). MGN, membranous glomerulonephritis; MCD, minimal change disease; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; NS, nephrotic syndrome.

<sup>b</sup> $P < 0.05$ .

Table 2. Clinical characteristics of patients with NS and associated glomerular disease after allogeneic HCT<sup>a</sup>

Pathology	Hematologic Diagnosis	Gender	GVHD		NS Presentation			NS Relationship to		NS Course			
			Acute	Chronic (mo)	Age (yr)	Date	Onset <sup>b</sup> (mo)	GVHD <sup>c</sup> (mo)	Medication Change <sup>d</sup> (mo)	Immuno-suppressive Treatment	Prognosis <sup>e</sup>		
MGN	CML (11)	M	Y	5	44	10/85	14	9	<1, CsA d/c	CsA	PR		
	AA (13)	M	Y	NR	20	NR	7	7	NR	S, CsA, Chloram	PR		
	CML (14)	M	Y	4	46	12/89	25	0	<1, CsA + S d/c	S, CsA	CR		
	ALL (15)	M	Y	6	21	06/93	12	0	N	S, Dipy	PR		
	TCL (17)	M	Y	12	19	11/93	27	15	NR	S, CsA <sup>g</sup> , Dipy	CR		
	CML (18)	M	NR	NR	27	07/94	12	NR	NR	S	PR		
	CML (19)	M	Y	11	40	04/97	11	0	NR	S, CsA <sup>g</sup> , CPP	PR		
	CML (20)	F	N	10	31	12/97	12	0	1, S + CsA t	S, CsA	PR		
	CML (23)	M	Y	N	45	03/95	9	9	6, CsA d/c	NR	NR		
	MM (25)	M	Y	N	55	12/98	22	22	6, CsA d/c	S, CsA	CR		
	CML (26)	F	Y	5	57	08/99	13	0	<1, CsA d/c	S	PR		
	CML (26)	M	Y	11	25	06/00	18	7	1, S d/c	S, CsA <sup>g</sup> , CPP, MMF	PR		
	AA (29)	F	N	7	21	08/01	21	14	6, CsA d/c	S, CsA	PR		
	AML/MDS (32)	F	Y	14	51	11/01	17	3	9, CsA d/c	S	PR		
	AA (33)	M	N	15	60	NR	15	0	1, CsA d/c	S, CsA	PR		
	PNH (34)	F	Y	4	24	02/02	26	22	NR, CsA d/c	Tac	CR		
	CML (35)	M	N	4	16	11/97	9	5	3, CsA d/c	S	PR		
	ALL (35)	M	Y	3	19	06/98	14	5	6, S + Tac d/c	S	PR		
	ALCL (37)	M	Y	6	13	03/02	11	0	1/3, S/MTX d/c	S	CR		
	AML M2 (40)	M	Y	N	42	NR	18	15	6, S t + CsA d/c	S, CsA	NR		
	CML (40)	M	Y	Y <sup>f</sup>	34	NR	24	0	NR	S, CsA	CR		
	NHL 4B (41)	M	N	9	32	NR	12	3	7, Tac d/c	S, Rit	PR		
	MM (41)	M	Y	14	53	NR	14	0	5, S + Tac t	MMF, Rit <sup>g</sup>	PR		
	RCC (43)	M	NR	6	55	NR	11	0	NR	S, CsA	NO		
	RCC (43)	F	NR	5	45	NR	11	0	NR	S, CsA, Rit	NO		
	RCC (43)	M	NR	27	55	NR	28	0	NR	S, CsA, Rit, IVIg, PLEx	PR		
	AML (43)	F	NR	4	43	NR	32	0	NR	S, CsA	NO		
	AML M2	M	Y	6	46	07/03	22	0	5, S + CsA d/c	S, Tac, MMF	CR		
	MCD	RA (16)	F	Y	N	10	11/93	10	11	<1, CsA d/c	S, CsA	CR	
		AA (21)	M	N	13	27	03/95	14	0	2, CsA d/c	S, CsA	CR	
		CML (24)	M	Y	4	42	06/98	5	2	1, S t	S	CR	
		AML M3 (27)	F	N	9	19	12/98	34	25	1, CsA d/c	S, CPP	CR	
		AML M2 (31)	F	N	N	48	NR	4	N	1, CsA d/c	CsA	CR	
		AA (36)	F	N	N	3	12/00	2	N	N	S, CsA, CPP, Miz	CR	
		CML (38)	M	Y	13	53	09/01	13	0	NR, S t	S, CsA	CR	
		AML M2 (40)	F	Y	N	31	NR	5	3	<1, S d/c (on CsA)	S, CsA	CR	
		AL (42)	F	N	N	33	NR	25	N	NR	S	CR	
		HL	M	N	6	31	07/03	6	0	<1, CsA d/c	S	PR	
		FSGS	CML (22)	F	Y	N	4	03/99	17	17	NR, CsA t	S	PR
		FSGS	CML	M	Y	N	42	05/98	62	61	N	None	PR <sup>h</sup>
FSGS		SCD	F	Y	N	18	11/97	24	23	N	S	NO	
ICGN	T-ALL (12)	M	Y	7	16	NR	7	0	1, S d/c	S	CR		
ICGN	ANLL M2 (12)	F	Y	6	14	09/85	6	0	3, S d/c	S, Aza	PR		
IgAN/CGN	bNKL/L (30)	M	Y	N	34	03/01	9	9	NR, CsA t	CsA	CR		
IgAN/CGN	MDS/RAEB (39)	M	Y	Y	61	2003	24	0	NR, CsA t	S, CPP	NR		
DPGN/CGN	CML (28)	M	N	3	14	09/99	46	0	N	S, CPP	PR		

<sup>a</sup>AA, aplastic anemia; AL, acute leukemia; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; ANLL, acute nonlymphoblastic leukemia; Aza, azathioprine; bNKL/L, blastic natural killer cell leukemia/lymphoma; CGN, crescentic glomerulonephritis; Chloram, chlorambucil; CML, chronic myelogenous leukemia; CPP, cyclophosphamide; CR, complete remission; CsA, cyclosporine A; d/c, discontinuation; DPGN, diffuse proliferative glomerulonephritis; Dipy, dipyrindamole; F, female; FSGS, focal segmental glomerulosclerosis; HL, Hodgkin's lymphoma; ICGN, immune complex-mediated glomerulonephritis; IgAN, IgA nephropathy; IVIg, intravenous Ig; M, male; MDS, myelodysplastic syndrome; MDS/RAEB, myelodysplastic syndrome/refractory anemia with excess blasts; Miz, mizoribine; MM, multiple myeloma; MMF, mycophenolate mofetil; MTX, methotrexate; N, no/not present; NHL 4B, non-Hodgkin's lymphoma stage IV B; NO, no response; NR, not reported; PLEx, plasma exchange; PNH, paroxysmal nocturnal hemoglobinuria; PR, partial remission; RA, refractory anemia; IgGA with Bence-Jones light chain proteinuria; RCC, renal cell carcinoma; Rit, rituximab; S, glucocorticosteroids; SCD, sickle cell disease; Tac, tacrolimus; T-ALL, T cell acute lymphoblastic leukemia; TCL, T cell lymphoma; Y, yes/present.

<sup>b</sup>Defined as NS onset after HCT.

<sup>c</sup>Defined as NS onset after extrarenal GVHD; 0, concomitant diagnosis of NS and GVHD.

<sup>d</sup>Defined as NS onset after medication change within 12 months; d/c, discontinuation (medication cessation after taper was followed by NS); t, taper (medication dose decrease was followed by NS).

<sup>e</sup>CR defined as (1) a report of resolution of NS, even if persistent proteinuria was noted, in absence of further description by the authors, or (2) a report of proteinuria of <0.5 g/d; PR defined as (1) a report of improvement, in absence of further description by the authors, or (2) a report of persistent proteinuria of >0.5 g/d or impaired renal function.

<sup>f</sup>Time of chronic GVHD not reported.

<sup>g</sup>Agent with which remission was achieved (if reported).

<sup>h</sup>Later chronic kidney disease progression.

chronic GVHD, and chronic GVHD is particularly prevalent in MGN cases (88 *versus* 50% in MCD). Time from HCT until chronic GVHD onset is identical between the MGN and MCD groups (not significant). The NS presentation is consistently described as obvious, a feature that undermines the probability of lead time bias as a result of early proteinuria detection because of close monitoring after HCT. The presenting creatinine and proteinuria values are the same for MGN and MCD (not significant). ANA titers are mostly reported as negative or low (data not shown), whereas less than one fifth of the cases (14–16,21,32,37,39,40) possess a titer of 1:160 or higher. The average age at NS presentation tends to be lower for MCD as compared with MGN (not significant). It would be speculative to predict that patients who are older at the time of HCT are more prone to MGN than to MCD as a complication, thereby imitating the age distribution of so-called primary glomerulopathies. The typical time period between HCT and NS is shorter for MCD (median 8 *versus* 14 mo for MGN;  $P = 0.04$ ). A confounding of overall results by gender (75% male patients for MGN *versus* 40% for MCD) and occurrence of acute GVHD (78% for MGN *versus* 40% for MCD) cannot be ruled out completely.

To characterize the occurrence of NS after HCT further, we examined the diverse case reports regarding the time intervals until NS diagnosis after GVHD and after immunosuppression decrease. Overall, chronic GVHD affects single or multiple organs in all groups (data not shown), mostly skin (54%), liver (32%), mucosa (24%), and gastrointestinal tract (17%). In 47% of all patients, a concomitant temporal relationship between GVHD and NS can be observed, as NS appears simultaneously with chronic GVHD. In the 47% with a report of preceding GVHD, a strong correlation between NS temporal distance to HCT and to chronic GVHD is found ( $P = 0$ , correlation coefficient 0.804). The potential conclusion that NS appears either simultaneously with GVHD or equally distanced from the HCT and the last GVHD event is difficult to explain pathophysiologically. This phenomenon needs to be reevaluated with larger patient numbers to rule out an effect of disparities in physicians' attention to GVHD findings at the time of NS and an effect of immunosuppression use as a result of various mechanisms of action and interaction. It may be proposed that the different pathogenesis of MGN and MCD plays a role, because the proportion of concomitant GVHD and NS is higher in MGN and the time period from last GVHD to NS has a tendency of being shorter, although without reaching statistical significance. In the combined MGN and MCD group, 56% within 3 mo and 60% within 5 mo exhibited a pattern of temporal association between most recent chronic GVHD diagnosis and NS occurrence.

The time course between cessation or tapering of immunosuppressive medication and onset of NS suggests the former as a risk factor. For joint consideration of tapering and cessation, this phenomenon can be observed in 58% overall within 9 mo after discontinuation of immunosuppression. The percentages increase to 63% in the combined MGN and MCD group and to even 70% in MCD patients, here within 2 mo only. These proportions were calculated with all cases in the denominator,

including those with missing values, and therefore may be falsely low; however, the true effect could also be obscured by recall bias, as case report authors may have overattributed NS occurrence to medication changes retrospectively. NS presents earlier after immunosuppression decrease in the case of MCD (median 1 *versus* 5 mo for MGN;  $P = 0.03$ ). In two of our four cases, the temporal relationship to NS is also close for both events, with concomitant diagnosis of chronic GVHD and discontinuation of immunosuppression in <1 and 5 mo before, respectively. Some of the references do not describe details about GVHD examinations or medication changes; therefore, a higher percentage of cases than reported may support the associations outlined above. On the basis of these relationships, the interpretation of glomerular disease as the manifestation of renal GVHD is conceivable. This suggests the possibility that NS may occasionally be the only manifestation of chronic GVHD in an HCT patient.

The seemingly good prognosis has to be weighed against the lack of comparable long-term follow-up time, on which the case report authors often do not comment. Whereas only 27 and 62% of the patients with MGN show complete and partial remission, respectively, almost all (90%) patients with MCD achieve complete remission, which likens the excellent prognosis to idiopathic MCD. Successful treatment options include glucocorticosteroids and CsA. Other agents that have been used in the past for GVHD and glomerular disease, respectively, seem to have therapeutic potential as well, such as cyclophosphamide, tacrolimus, mycophenolate mofetil, and rituximab. A total of 56% of cases can be associated with a dosing change of CsA and 36% of a glucocorticosteroid; however, the relation between the two medications is reversed for treatment, as 51% of patients receive CsA and 87% receive steroids. This discrepancy may be explained by the frequent use of CsA as GVHD prophylaxis for several months after HCT and the comfort with which steroids are used for NS treatment. The significance of the incongruity remains intangible as the question continues to be unsettled whether a steroid-CsA combination for extensive GVHD offers survival benefits over steroids alone or just ameliorates steroid side effects (52–54).

A cohort study (43) identified nonmyeloablative HCT as a risk factor for NS, because seven of 163 consecutive patients from 1997 to 2003 developed this complication as opposed to none of 118 patients after myeloablative HCT, with comparable rates of chronic GVHD during the same period. Because the vast majority (>80%) of all cases reviewed here, aside from the mentioned cohort study, were myeloablative (data not shown) and the preparative regimen was not reported in several of the remaining cases, the cohort study's authors' claim that reduced intensity conditioning poses a greater risk for NS than myeloablative preparation can neither be supported nor challenged by this analysis. Follow-up of larger cohorts is mandatory to define potential NS risk factors definitively, such as presence or history of GVHD, immunosuppression change, conditioning regimen, and degree of mixed hematopoietic chimerism. An inquiry to the International Bone Marrow Transplant Registry, which collects data on approximately 40% of allogeneic HCT worldwide, yielded no opportunity to study the association

between HCT and NS easily on a large-scale epidemiologic level, because the registry does not routinely collect data regarding specific renal complications.

Regarding further evidence for a link between HCT and glomerular disease, a finding of glomerular sclerosis in 73% of patients at autopsy is suggestive in a study of 26 patients (55). The authors' hypothesis that acute or chronic GVHD is associated with tubulitis could not be corroborated in this study. This fact underscores the lack of tubulitis in the reviewed biopsy specimens, although one separate case report (56) links tubulitis to GVHD after steroid and CsA withdrawal in the absence of glomerular changes. Japanese HCT recipients were evaluated by questionnaires for renal complications (57), which occurred in 51 of 2136 patients. Although the majority of adverse effects was seen within the first 120 d (36 patients), no case of NS was reported then. However, NS was the most common renal abnormality (eight of 15 patients) after 180 d. An association between chronic GVHD and MGN after HCT was also suggested by the preliminary results of a German study (58) in which all patients with glomerular proteinuria  $>1$  g/d 1 yr after HCT underwent biopsy (19 of 580 patients followed), resulting in a diagnosis of MGN in approximately one third of cases (six patients). Other histologic findings were not reported in the abstract, and only patients with proteinuria of  $>8$  g/d were treated with immunosuppression. Therefore, subjecting all patients to biopsies with a sole indication of non-nephrotic-range proteinuria after HCT does not appear clinically warranted. At this time, it seems prudent to follow patients regularly with urine dipsticks to screen for proteinuria after HCT. Referral to a nephrologist is encouraged to determine indications for a kidney biopsy on the basis of all clinical characteristics of the presentation, including a full urine examination.

Clinical features in chronic GVHD, outside the kidney, are comparable to autoimmune diseases (59), such as systemic lupus erythematosus (SLE) and scleroderma. Mice after allogeneic stem cell injection have been studied as an SLE model in the distant past (60). The histologic spectrum of renal disease after HCT, albeit with preference of MGN and MCD and for the most part without significant ANA titers, is reminiscent of the variety of lupus nephritis manifestations. Production of glomerulotoxic cytokines and development of autoantibodies in chronic GVHD (61) could make this disease a lupus-resembling entity. A sole report (31) of cytokine monitoring after HCT revealed an increased production of IFN- $\gamma$  and TNF- $\alpha$  but not IL-4 during the ensuing NS. It remains to be proven that renal lesions of GVHD can mimic most or all of the various pathologic findings of autoimmune diseases in the kidney, such as those found in SLE (62), for example MGN; MCD; mesangial immune deposits; focal, diffuse, segmental, or global glomerular lesions and sclerosis; immune aggregates in the tubular basement membrane and in intrarenal vessels; and true vasculitis.

At this time, the pathogenesis of GVHD-related glomerular disease and NS after HCT remains elusive. The most common diagnoses, MGN, MCD, and FSGS, are typical culprits of nephrotic-range proteinuria with glomerular epithelial cells as their target of injury. The existence of a circulating permeability

factor secreted by T cells has been postulated for subsets of both MCD (63) and FSGS (64). MGN is also regarded as a primarily podocyte-linked disease (65,66), because it is associated with subepithelial immune deposits of IgG, C3, and the complement membrane attack complex and because it can be induced by antibodies against antigenic targets on podocytes in the murine model of Heyman nephritis (67). Rare histopathologic correlates seen here affect other glomerular compartments and cell types, such as the mesangial space in IgA nephropathy and the endothelium, mesangium, and infiltrating immune cells in diffuse proliferative and crescentic glomerulonephritis. Possible but diverse immune routes of NS pathogenesis after HCT therefore involve T and B cells and, only locally, monocytes and macrophages. Traditionally, HCT has been used to achieve complete eradication of host immune cells; therefore, it may be hypothesized that donor-derived hematopoietic cells can be the origin of all immune-linked glomerular diseases. Recently, mixed chimerism after HCT has been used for certain conditions, and persisting host B and plasma cells have been thought to increase the risk for NS (43), although their contribution to the proposed GVHD aspect of the disease remains undefined.

## Conclusion

Although chronic GVHD has been found in many organ systems, the effect of GVHD on the kidney has not been recognized widely in the past. The reviewed literature supports the existence of the entity of renal GVHD, specified as glomerular lesions with NS clinically. The case reports are unlikely to have accumulated as a result of publication bias, in favor of occurrence of two unrelated rare events, because of the temporal associations of glomerular alterations with GVHD and medication changes outlined above. This type of renal disease is distinct from progression of nephropathy that develops as a result of injury surrounding the HCT process itself. With the increasing use of HCT for malignant and nonmalignant conditions, both nephrologists and oncologists will more frequently recognize NS as a manifestation of GVHD. The pathophysiology of this association is unclear thus far and warrants further investigation. Specifically, the link of GVHD affecting the kidney to renal manifestations of autoimmune disease such as SLE needs to be elucidated.

## Acknowledgments

K.B. is the recipient of a National Kidney Foundation Postdoctoral Research Fellowship from July 2005 to June 2007.

Preliminary results of this study were presented in poster format at the American Society of Nephrology Annual Meeting, Philadelphia, PA, November 8 to 13, 2005.

We would like to thank Masahiko Nagahama, MD, Department of Medicine, Pennsylvania Hospital, Philadelphia, and Taku Kambayashi, MD, PhD, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, for translation of references from the Japanese literature. We thank Cooper Hospital (Camden, NJ) for the opportunity to review pathology data and health information for one case. We wish to thank Marta E. Guttenberg, MD, and Pierre A. Russo, MD, Anatomic Pathology, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, for the repeat biopsy review of a case.

We apologize to those authors whose works could not be cited because of publication during the review period and restraints on the number of references.

## References

- Cohen EP: Renal failure after bone-marrow transplantation. *Lancet* 6: 6–7, 2001
- Cohen EP, Lawton CA, Moulder JE, Becker CG, Ash RC: Clinical course of late-onset bone marrow transplant nephropathy. *Nephron* 64: 626–635, 1993
- Cruz DN, Perazella MA, Mahnensmith RL: Bone marrow transplant nephropathy: A case report and review of the literature. *J Am Soc Nephrol* 8: 166–173, 1997
- Reddy P: Pathophysiology of acute graft-versus-host disease. *Hematol Oncol* 21: 149–161, 2003
- Ferrara JL, Cooke KR, Teshima T: The pathophysiology of acute graft-versus-host disease. *Int J Hematol* 78: 181–187, 2003
- Bhushan V, Collins RH Jr: Chronic graft-vs-host disease. *JAMA* 19: 2599–2603, 2003
- Eagen JW, Lewis EJ: Glomerulopathies of neoplasia. *Kidney Int* 11: 297–303, 1977
- Alpers CE, Cotran RS: Neoplasia and glomerular injury. *Kidney Int* 30: 465–473, 1986
- Korzets Z, Golan E, Manor Y, Schneider M, Bernheim J: Spontaneously remitting minimal change nephropathy preceding a relapse of Hodgkin's disease by 19 months. *Clin Nephrol* 38: 125–127, 1992
- Chiang KY, Lazarus HM: Should we be performing more combined hematopoietic stem cell plus solid organ transplants? *Bone Marrow Transplant* 31: 633–642, 2003
- Hiesse C, Goldschmidt E, Santelli G, Charpentier B, Machover D, Fries D: Membranous nephropathy in a bone marrow transplant recipient. *Am J Kidney Dis* 11: 188–191, 1988
- Gomez-Garcia P, Herrera-Arroyo C, Torres-Gomez A, Gomez-Carrasco J, Aljama-Garcia P, Lopez-Rubio F, Martinez-Guibelalde F, Fornes-Torres G, Rojas-Contreras R: Renal involvement in chronic graft-versus-host disease: A report of two cases. *Bone Marrow Transplant* 3: 357–362, 1988
- Muller GA, Muller CA, Markovic-Lipkowski J, Bross-Bach U, Schmidt H, Ehniger G, Bohle A, Rislser T: Membranous nephropathy after bone marrow transplantation in cyclosporin treatment. *Nephron* 51: 555–556, 1989
- Barbara JA, Thomas AC, Smith PS, Gillis D, Ho JO, Woodroffe AJ: Membranous nephropathy with graft-versus-host disease in a bone marrow transplant recipient. *Clin Nephrol* 37: 115–118, 1992
- Sato N, Kishi K, Yagisawa K, Kasama J, Karasawa R, Shimada H, Nishi S, Ueno M, Ito K, Koike T, Takahashi H, Moriyama Y, Arakawa M, Shibata A: Nephrotic syndrome in a bone marrow transplant recipient with chronic graft-versus-host disease. *Bone Marrow Transplant* 16: 303–305, 1995
- Walker JV, Morich D, Anasetti C: Minimal-change nephrotic syndrome after cyclosporine withdrawal in a marrow transplant recipient. *Am J Kidney Dis* 26: 532–534, 1995
- Haseyama K, Watanabe J, Oda T, Katoh S, Suzuki N, Kudoh T, Chiba S: Nephrotic syndrome related to chronic graft versus host disease after allogeneic bone marrow transplantation in a patient with malignant lymphoma [in Japanese]. *Rinsho Ketsueki* 37: 1383–1388, 1996
- Yabana M, Takagi N, Kihara M, Muto R, Tamura K, Maemoto S, Minamisawa M, Nakatani Y, Ishii M: A case of nephrotic syndrome after bone marrow transplantation [in Japanese]. *Nippon Jinzo Gakkai Shi* 39: 414–420, 1997
- Yorioka N, Taniguchi Y, Shimote K, Komo T, Yamakido M, Hyodo H, Kimura A, Taguchi T: Membranous nephropathy with chronic graft-versus-host disease in a bone marrow transplant recipient. *Nephron* 80: 371–372, 1998
- Nergizoglu G, Keven K, Ates K, Ustun C, Tulunay O, Beksac M, Karatan O, Ertug AE: Chronic graft-versus-host disease complicated by membranous glomerulonephritis. *Nephrol Dial Transplant* 14: 2461–2463, 1999
- Oliveira JS, Bahia D, Franco M, Balda C, Stella S, Kerbaui J: Nephrotic syndrome as a clinical manifestation of graft-versus-host disease (GVHD) in a marrow transplant recipient after cyclosporine withdrawal. *Bone Marrow Transplant* 23: 99–101, 1999
- Chien YH, Lin KH, Lee TY, Lu MY, Tsau YK: Nephrotic syndrome in a bone marrow transplant recipient without chronic graft-versus-host disease. *J Formos Med Assoc* 99: 503–506, 2000
- Ohsawa I, Ohi H, Fujita T, Endo M, Ito T, Sawada U, Yamaguchi Y: Glomerular and extraglomerular immune complex deposits in a bone marrow transplant recipient. *Am J Kidney Dis* 36: E3, 2000
- Ishizuka Y, Yokota A, Hara S, Nakaseko C, Matsuura Y, Nishimura M, Saitoh Y: Transient nephrotic syndrome after allogeneic bone marrow transplantation for chronic myelogenous leukemia [in Japanese]. *Rinsho Ketsueki* 42: 321–327, 2001
- Rossi L, Cardarelli F, Vampa ML, Buzio C, Olivetti G: Membranous glomerulonephritis after haematopoietic cell transplantation for multiple myeloma. *Nephron* 88: 260–263, 2001
- Lin J, Markowitz GS, Nicolaidis M, Hesdorffer CH, Appel GB, D'Agati VD, Savage DG: Membranous glomerulopathy associated with graft-versus-host disease following allogeneic stem cell transplantation. Report of 2 cases and review of the literature. *Am J Nephrol* 21: 351–356, 2001
- Akar H, Keven K, Celebi H, Orhan D, Nergizoglu G, Erbay B, Tulunay O, Ozcan M, Erturk S: Nephrotic syndrome after allogeneic peripheral blood stem cell transplantation. *J Nephrol* 15: 79–82, 2002
- Suehiro T, Masutani K, Yokoyama M, Tokumoto M, Tsuruya K, Fukuda K, Kanai H, Katafuchi R, Nagatoshi Y, Hirakata H: Diffuse proliferative glomerulonephritis after bone marrow transplantation. *Clin Nephrol* 58: 231–237, 2002
- Kim KW, Yoon CH, Kay CS, Kim HJ, Suh KS, Kim SY, Park SY: Membranous nephropathy after allogeneic hematopoietic stem cell transplantation in a patient with aplastic anemia: a case report. *J Korean Med Sci* 18: 287–289, 2003
- Kimura S, Horie A, Hiki Y, Yamamoto C, Suzuki S, Kuroda J, Deguchi M, Kato G, Karasuno T, Hiraoka A, Yoshikawa T, Maekawa T: Nephrotic syndrome with crescent formation and massive IgA deposition following allogeneic bone marrow transplantation for natural killer cell leukemia/lymphoma. *Blood* 101: 4219–4221, 2003

31. Seconi J, Watt V, Ritchie DS: Nephrotic syndrome following allogeneic stem cell transplantation associated with increased production of TNF-alpha and interferon-gamma by donor T cells. *Bone Marrow Transplant* 32: 447–450, 2003
32. Miyazaki Y, Mori Y, Kishimoto N, Matsumoto N, Zen K, Amakawa R, Kishimoto Y, Fukuhara S: Membranous nephropathy associated with donor lymphocyte infusion following allogeneic bone marrow transplantation. *Int J Hematol* 78: 262–265, 2003
33. Bernis C, Camara R, Garcia Sanchez A, Martinez MA, Selgas R: Nephrotic syndrome in a bone marrow transplant recipient after cyclosporine withdrawal. *Nephrol Dial Transplant* 18: 2457, 2003
34. Lee GW, Lee JH, Kim SB, Yu ES, Lee JL, Ryu MH, Kim E, Choi SJ, Kim WK, Lee JS, Lee KH: Membranous glomerulopathy as a manifestation of chronic graft-versus-host-disease after non-myeloablative stem cell transplantation in a patient with paroxysmal nocturnal hemoglobinuria. *J Korean Med Sci* 18: 901–904, 2003
35. Tsutsumi C, Miyazaki Y, Fukushima T, Yoshida S, Taguchi J, Miyake C, Miyazaki M, Kohno S, Jinnai I, Tomonaga M: Membranous nephropathy after allogeneic stem cell transplantation: Report of 2 cases. *Int J Hematol* 79: 193–197, 2004
36. Morisada N, Okita S, Sato T, Miyaji R, Kamizono J, Shimono M, Osajima A, Kaizu K, Asayama K, Shirahata A: Girl with nephrotic syndrome after peripheral blood stem cell transplantation. *Pediatr Int* 46: 480–483, 2004
37. Park YD, Hamada M, Higuchi B, Kishimoto T, Inagaki J, Nishiguchi M, Shimoyama H, Nakajima M, Nakagawa A, Yoshioka A: Membranous nephropathy following allogeneic peripheral blood stem cell transplantation in a boy with anaplastic large cell lymphoma [in Japanese]. *Rinsho Ketsueki* 45: 1193–1197, 2004
38. Ikee R, Yamamoto K, Kushiyama T, Imakiire T, Suzuki S, Miura S: Recurrent nephrotic syndrome associated with graft-versus-host disease. *Bone Marrow Transplant* 34: 1005–1006, 2004
39. Chan GS, Lam MF, Au WY, Tse KC, Chan TM, Lai KN, Chan KW: IgA nephropathy complicating graft-versus-host disease, another nephropathy causing nephrotic syndrome after bone marrow transplantation. *Histopathology* 45: 648–651, 2004
40. Stevenson WS, Nankivell BJ, Hertzberg MS: Nephrotic syndrome after stem cell transplantation. *Clin Transplant* 19: 141–144, 2005
41. Rao PS: Nephrotic syndrome in patients with peripheral blood stem cell transplant. *Am J Kidney Dis* 45: 780–785, 2005
42. Romagnani P, Lazzeri E, Mazzinghi B, Lasagni L, Guidi S, Bosi A, Cirami C, Salvadori M: Nephrotic syndrome and renal failure after allogeneic stem cell transplantation: Novel molecular diagnostic tools for a challenging differential diagnosis. *Am J Kidney Dis* 46: 550–556, 2005
43. Srinivasan R, Balow JE, Sabnis S, Lundqvist A, Igarashi T, Takahashi Y, Austin H, Tisdale J, Barrett J, Geller N, Childs R: Nephrotic syndrome: An under-recognised immune-mediated complication of non-myeloablative allogeneic haematopoietic cell transplantation. *Br J Haematol* 131: 74–79, 2005
44. Arat M, Arslan O, Beksac M, Keven K, Nergizoglu G, Erturk S: Hematopoietic cell transplantation-related nephropathy. *Am J Kidney Dis* 38: 218–219, 2001
45. Yu J, Cui R, Tong S: Membranous nephropathy after allogeneic peripheral blood hematopoietic stem cell transplantation: Clinicopathologic manifestations of a rare chronic GVHD [in Chinese]. *Zhonghua Xue Ye Xue Za Zhi* 22: 415–417, 2001
46. Sato Y, Hara S, Fujimoto S, Yamada K, Sakamaki H, Eto T: Minimal change nephrotic syndrome after allogeneic hematopoietic stem cell transplantation. *Intern Med* 43: 512–515, 2004
47. Kingdon EJ, Johnston RE, Pawson R, Prentice HG, Potter MN, Burns A, Powis SH: ANCA +ve vasculitis after autologous PBSC transplantation. *Nephrol Dial Transplant* 17: 285–287, 2002
48. Nouri-Majelan N, Sanadgol H, Ghafari A, Rahimian M, Najafi F, Mortazavizadeh M, Moghaddasi S: Antineutrophil cytoplasmic antibody-associated glomerulonephritis in chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Transplant Proc* 37: 3213–3215, 2005
49. Sakarcin A, Neuberg RW, McRedmond KP, Islek I: Membranoproliferative glomerulonephritis develops in a child with autologous stem cell transplant. *Am J Kidney Dis* 40: E19, 2002
50. Imai C, Kakihara T, Iwabuchi H, Tanaka A, Furukawa T, Uchiyama M: Glomerular vasculopathy after unrelated cord blood transplantation. *Pediatr Nephrol* 18: 399–402, 2003
51. Cutler C, Giri S, Jeyapalan S, Paniagua D, Viswanathan A, Antin JH: Acute and chronic graft-versus-host disease after allogeneic peripheral-blood stem-cell and bone marrow transplantation: a meta-analysis. *J Clin Oncol* 19: 3685–3691, 2001
52. Sullivan KM, Witherspoon RP, Storb R, Deeg HJ, Dahlberg S, Sanders JE, Appelbaum FR, Doney KC, Weiden P, Anasetti C, Loughran TP, Hill R, Shields A, Yee G, Shulman H, Nims J, Strom S, Thomas ED: Alternating-day cyclosporine and prednisone for treatment of high-risk chronic graft-versus-host disease. *Blood* 72: 555–561, 1988
53. Deeg HJ, Lin D, Leisenring W, Boeckh M, Anasetti C, Appelbaum FR, Chauncey TR, Doney K, Flowers M, Martin P, Nash R, Schoch G, Sullivan KM, Witherspoon RP, Storb R: Cyclosporine or cyclosporine plus methylprednisolone for prophylaxis of graft-versus-host disease: A prospective, randomized trial. *Blood* 89: 3880–3887, 1997
54. Koc S, Leisenring W, Flowers ME, Anasetti C, Deeg HJ, Nash RA, Sanders JE, Witherspoon RP, Storb R, Appelbaum FR, Martin PJ: Therapy for chronic graft-versus-host disease: A randomized trial comparing cyclosporine plus prednisone versus prednisone alone. *Blood* 100: 48–51, 2002
55. El-Seisi S, Gupta R, Clase CM, Forrest DL, Milandinovic M, Couban S: Renal pathology at autopsy in patients who died after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 9: 683–688, 2003
56. Homma CI, Kami M, Masuo S, Sakiyama M, Kojima R, Hori A, Kusumi E, Katori H, Takeuchi K, Kishi Y, Murashige N, Kim SW, Takaue Y, Mitamura T: Graft-versus-host disease of the kidney after rapid tapering of cyclosporin following reduced intensity hematopoietic stem cell transplantation. *Bone Marrow Transplant* 35: 929–930, 2005
57. Imai H, Oyama Y, Miura AB, Endoh M, Sakai H: Hemato-

- poietic cell transplantation-related nephropathy in Japan. *Am J Kidney Dis* 36: 474–480, 2000
58. Herget-Rosenthal S, Elmaagacli A, Struning C, Beelen D, Philipp T, Kribben A: Membranous nephropathy after allogeneic hematopoietic stem cell transplantation [Abstract]. *J Am Soc Nephrol* 15: 10A–11A, 2004
  59. Hartert A, Willenbacher W, Gunzelmann S, Roemer E, Basara N, Fauser AA, Kiehl MG: Successful treatment of thrombocytopenia and hemolytic anemia with IvIG in a patient with lupus-like syndrome after mismatched related PBSCT. *Bone Marrow Transplant* 27: 337–340, 2001
  60. Van Rappard-Van Der Veen FM, Radaszkiewicz T, Terraneo L, Gleichmann E: Attempts at standardization of lupus-like graft-vs-host disease: Inadvertent repopulation by DBA/2 spleen cells of H-2-different nonirradiated F1 mice. *J Immunol* 130: 2693–2701, 1983
  61. Wechalekar A, Cranfield T, Sinclair D, Ganzckowski M: Occurrence of autoantibodies in chronic graft vs. host disease after allogeneic stem cell transplantation. *Clin Lab Haematol* 27: 247–249, 2005
  62. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, Balow JE, Bruijn JA, Cook T, Ferrario F, Fogo AB, Ginzler EM, Hebert L, Hill G, Hill P, Jennette JC, Kong NC, Lesavre P, Lockshin M, Looi LM, Makino H, Moura LA, Nagata M: International Society of Nephrology Working Group on the Classification of Lupus Nephritis; Renal Pathology Society Working Group on the Classification of Lupus Nephritis: The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 15: 241–250, 2004
  63. Koyama A, Fujisaki M, Kobayashi M, Igarashi M, Narita M: A glomerular permeability factor produced by human T cell hybridomas. *Kidney Int* 40: 453–460, 1991
  64. Dantal J, Bigot E, Bogers W, Testa A, Kriaa F, Jacques Y, Hurault de Ligny B, Niaudet P, Charpentier B, Souillou JP: Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. *N Engl J Med* 330: 7–14, 1994
  65. Debiec H, Nauta J, Coulet F, van der Burg M, Guignonis V, Schurmans T, de Heer E, Soubrier F, Janssen F, Ronco P: Role of truncating mutations in MME gene in fetomaternal alloimmunisation and antenatal glomerulopathies. *Lancet* 364: 1252–1259, 2004
  66. Kerjaschki D: Pathomechanisms and molecular basis of membranous glomerulopathy. *Lancet* 364: 1194–1196, 2004
  67. Saito A, Yamazaki H, Rader K, Nakatani A, Ullrich R, Kerjaschki D, Orlando RA, Farquhar MG: Mapping rat megalin: The second cluster of ligand binding repeats contains a 46-amino acid pathogenic epitope involved in the formation of immune deposits in Heymann nephritis. *Proc Natl Acad Sci U S A* 93: 8601–8605, 1996

Successful solid organ and cellular transplants have led to survival for many patients who would have succumbed to their primary hematologic neoplasms. Although myeloablative hemopoietic cell transplant is much more successful in 2006, toxicities due to treatment are increasingly apparent. The review of chronic kidney disease in survivors of such transplants is highlighted in *JASN* this month as a Disease of the Month (Hingorani, pp. 1995–2005). This provides an extensive review of the subject, which will be relevant for consultant nephrologists.