Kidney Biopsy Findings Among Allogenic Hematopoietic Stem Cell Transplant Recipients With Kidney Injury: A Case Series

Guillaume Roy, Ilinca Iordachescu, Virginie Royal, Caroline Lamarche, Imran Ahmad, Annie-Claire Nadeau-Fredette, and Louis-Philippe Laurin

Rationale and Objective: The incidence of kidney disease is high in patients after allogeneic hematopoietic cell transplantation (aHCT). Although rarely performed, kidney biopsy may be useful to make a precise diagnosis because several mechanisms and risk factors can be involved, and to adjust the treatment accordingly. This case series aimed to report the spectrum of biopsy findings from patients with kidney injury after aHCT.

Study Design: Single-center retrospective case series.

Setting and Participants: All individuals who underwent a native kidney biopsy, among all adult patients who received aHCT in a tertiary hospital in Montreal (Canada) from January 1, 2010, to December 31, 2020, were identified, and the clinical data were extracted from their medical records.

Results: A total of 17 patients were included. Indications for biopsy included acute kidney injury (n=6), chronic kidney disease (n=5), nephrotic syndrome (n=4), and subnephrotic proteinuria (n=2). Pathologic findings from the kidney biopsy were heterogenous: 10 patients showed evidence of thrombotic microangiopathy (TMA), 5 of acute tubular injury, and 4 of membranous nephropathy. Cases of acute interstitial nephritis, BK virus nephropathy, immune complex nephropathy, focal and segmental glomerulosclerosis, minimal change disease, and karyomegalic-like interstitial nephritis were also described.

Limitations: There was no systematic kidney biopsy performed for all patients with kidney injury after aHCT. Only a small proportion of patients with kidney damage underwent biopsy, making the results less generalizable.

Conclusions: Kidney biopsy is useful in patients with kidney disease after aHCT to make a precise diagnosis and tailor therapy accordingly. This series is one of the few published studies describing pathologic findings of biopsies performed after aHCT in the context of acute kidney injury and chronic kidney disease. TMA was widely present on biopsy even when there was no clinical suspicion of such a diagnosis, suggesting that the current clinical criteria for a diagnosis of TMA are not sensitive enough for kidney-limited TMA.

Complete author and article information provided before references.

Correspondence to L.-P. Laurin (louis-philippe.laurin@umontreal.ca)

Kidney Med. 5(7):100674. Published online May 16, 2023.

doi: 10.1016/j.xkme.2023.100674

Allogeneic hematopoietic cell transplantation (aHCT) is the curative treatment of many hematologic and immune disorders. Although many aHCT complications are commonly recognized by physicians, a less-known but still-frequent complication is kidney disease, with up to 36% of patients developing acute kidney injury (AKI) in the first 100 days after transplantation.[1] Chronic kidney disease (CKD) is also frequent, with ∼44% of patients reported as having new-onset CKD after aHCT.[2] Numerous cases of nephrotic syndrome have also been reported after aHCT, which is believed to represent kidney graft-versus-host disease (GVHD).[3] In addition to the typical causes of AKI and CKD, other causative factor, such as medication toxicity, sinusoidal obstruction syndrome, viral nephropathy, and thrombotic microangiopathy (TMA), can be present in this population. Kidney GVHD is also suspected to exist but has not been described as extensively as for other organs.

Considering the wide array of causative factors causing kidney disease in patients who underwent aHCT, native kidney biopsy (NKB) is generally useful to make an accurate diagnosis. However, even with a high incidence of kidney disease after aHCT, NKB is reported to be performed in only 0.5% to 4.3% of the patients.[4] A dozen of case series have been published on kidney biopsy results in patients with nephrotic syndrome after aHCT, but reports of pathologic findings in patients experiencing AKI or CKD remain scarce in the literature. In this article, we report a case series of 17 patients who underwent a NKB after aHCT from various clinical presentations.

METHODS

Patient Selection

Among patients who received aHCT from January 1, 2010, to December 31, 2020, at Maisonneuve-Rosemont Hospital, a tertiary care teaching hospital in Montreal, Canada, all those aged 18 years or older with NKB performed after their aHCT were selected. No time limitation was imposed between aHCT and kidney biopsy. The study was approved by our institution's research ethics committee (No 2021-2633), in agreement with the tenets of the Declaration of Helsinki.

Data Collection

Data were collected by reviewing medical records and included demographics, kidney disease presentation, comorbidities, medications, details regarding aHCT, and pathologic characteristics of the kidney biopsy. All authors had access to primary clinical trial data.

PLAIN LANGUAGE SUMMARY

Kidney diseases are frequent after allogeneic hematopoietic cell transplantation (aHCT), but the etiology is often difficult to define because multiple mechanisms may be involved in this population. This case series of kidney biopsies of patients after allogeneic hematopoietic cell transplantation gives a general idea of the different causative factors encountered in this population. Kidney-isolated thrombotic microangiopathy was frequently found and was usually not suspected clinically before the kidney biopsy. The result of the kidney biopsy was generally not in concordant with what was expected by the clinician, suggesting that kidney biopsies are relevant in this population and should be performed more frequently to help tailor treatment of patients.

Proteinuria was quantified using a 24-hour urinary collection; if not available, the urinary protein-creatinine ratio was used. The glomerular filtration rate (GFR) was estimated by applying the Chronic Kidney Disease Epidemiology Collaboration formula.[5] AKI was defined as an increase of serum creatinine concentration of ≥0.3 mg/dL within 48 hours or ≥50% in 7 days.[6] CKD was determined as a GFR of ≤60 mL/min/1.73 m^2 on at least 2 measures covering more than 3 consecutive months.[7] Proteinuria of ≥3.5 g/d and serum albumin concentration of ≤3.5 g/dL were used to characterize nephrotic syndrome.

Treatment outcomes for nephrotic syndrome were categorized as complete remission or partial remission. Complete remission was defined as 24-hour proteinuria of ≤0.5 g/d, serum albumin concentration of ≥3.5 g/dL, and stable GFR. Partial remission was defined as 24-hour proteinuria of ≤2.5 g/d or a reduction of ≥50%, serum albumin concentration of ≥3.0 g/dL, and stable GFR.

Pathology

Standard processing of kidney biopsy specimens for light microscopy, immunofluorescence—IgG, IgA, IgM, C3, C1q, fibrinogen, κ, and λ, and electron microscopy was performed. Additional studies, such as immunofluorescence for C4d in cases of TMA, and immunohistochemistry for PLA2R (M-type phospholipase A2 receptor) in cases of membranous nephropathy (MN), were performed. Immunohistochemistry studies for simian virus 40 (SV40), cytomegalovirus, adenovirus, Epstein-Barr virus, herpes simplex virus (HSV)-1, and HSV-2 were performed when relevant.

Review of Literature

A review of literature was performed to identify all case series published in English or French, which included a minimum of 3 adult patients (≥18 years or older) who underwent NKB after aHCT. On March 25, 2022, the following terms were searched on PubMed and Embase: "hematopoietic cell transplant* and (((kidney or renal) and (biops* or pathology)) or nephrotic syndrome)". The following MeSH terms were also added on PubMed: "hematopoietic stem cell transplantation", "kidney/pathology", "kidney diseases/pathology" and "kidney glomerulus/pathology." Autopsy specimens were excluded. The articles in which data were not detailed enough to exclude individual patients who were not fulfilling this review's criteria (eg, autologous stem cell transplant or children) were also excluded.

RESULTS

Patient Characteristics

Of all 879 patients who received aHCT at Maisonneuve-Rosemont Hospital between January 1, 2010, and December 31, 2020, 17 underwent NKB after transplantation (see Tables 1 and 2 for baseline characteristics). All patients showed normal kidney function before aHCT except patient 6 who showed a baseline serum creatinine concentration of 1.45 mg/dL (estimated GFR of 50 mL/min/1.73 m^2). The most frequent indications for aHCT were acute myeloid leukemia (5 patients), chronic lymphocytic leukemia (3 patients), and Hodgkin lymphoma (3 patients). A total of 12 patients received peripheral blood hematopoietic cell transplant, 3 received umbilical cord blood transplant, and 2 received bone marrow transplant. Acute and chronic GVHD was diagnosed before kidney biopsy in 10 patients each.

Indications for kidney biopsy were diverse: AKI in 6 patients, CKD in 5 patients, nephrotic syndrome in 4 patients, and subnephrotic proteinuria in 2 patients. Pathologic findings are summarized in Table 3. Features of TMA were found in 10 patients, and 5 patients showed acute tubular injury (ATI). Other diagnoses included MN in 4 patients, and single cases of acute interstitial nephritis (AIN), BK virus nephropathy, focal and segmental glomerulosclerosis (FSGS), minimal change disease (MCD), and karyomegalic-like interstitial nephritis. No significant complication (major bleeding, need for blood transfusion or renal artery embolization, prolongation of hospitalization, or biopsy-related visit to the emergency room) resulted from kidney biopsy.

Chronic Kidney Disease

Among the 5 patients who underwent biopsy because of CKD [median time between aHCT and kidney biopsy of 15 months (range, 14-46 months)], all showed histologic features suggestive of TMA (Fig 1). Among the patients treated with glucocorticoids or rituximab, none improved their kidney function after treatment. Patient 14 showed a reduction in proteinuria after rituximab,

Table 1. Patients Demographics and aHCT Characteristics

Patient	Age at Biopsy, y	Sex	aHCT Indication	aHCT Type	Conditioning Regimen	GVHD Prophylaxis (Duration if Not Continued as GVHD Treatment[a])	aGVHD (site)	cGVHD (Site, Moment of Appearance Before NKB)	GVHD Treatments Received	GVHD Systemic Treatment at Time of NKB
1	28	F	AML	PBHCT, unrelated	Cyclophosphamide, TBI	ATG, MMF, tacrolimus	Yes (gastro-intestinal, skin)	NA	Corticosteroids, MMF, tacrolimus	Corticosteroids, tacrolimus
2	40	M	MDS	PBHCT, unrelated	Busulfan, cyclophosphamide	Methotrexate, tacrolimus	Yes (gastro-intestinal)	Yes (gastro-intestinal, 10 m)	Corticosteroids, MMF, pentostatin, sirolimus, tacrolimus	Corticosteroids, MMF
3	57	M	NHL	PBHCT, related	Cyclophosphamide, TBI	Cyclosporine, methotrexate	Yes (liver, skin)	Yes (eyes, mouth and skin, 63 m; serositis, 43 m; arthritis, 21 m)	Bortezomib, corticosteroids, cyclosporine, ECP, imatinib, MMF, rituximab, ruxolitinib, sirolimus, tacrolimus	Corticosteroids, MMF, ruxolitinib, tacrolimus
4	59	M	AML	BMT, unrelated	Busulfan, cyclophosphamide	Methotrexate, tacrolimus (105 d)	No	No	NA	NA
5	24	M	HL	PBHCT, unrelated	Fludarabine, TBI	MMF (100 d), tacrolimus	No	Yes (mouth and skin, 17 m)	Corticosteroids, sirolimus, tacrolimus	Corticosteroids, sirolimus
6	63	M	CLL	PBHCT, related	Fludarabine, melphalan	Cyclosporine (170 d), methotrexate	Yes (skin)	Yes (eyes and skin, 13 m; mouth, 11 m)	Corticosteroids, cyclosporine	Corticosteroids
7	62	M	AML	PBHCT, related	Fludarabine, busulfan	Cyclosporine, methotrexate	Yes (gastro-intestinal)	Yes (skin and liver, 4 m)	Corticosteroids, cyclosporine	Corticosteroids, cyclosporine
8	27	M	AML	BMT, unrelated	Busulfan, cyclophosphamide	ATG, methotrexate, tacrolimus (120 d)	No	No	NA	NA
9	30	F	ALL	PBHCT, related	Fludarabine, thiotepa, TBI	ATG, T-cell depletion	Yes (skin)	No	NA	NA
10	51	M	CLL	PBHCT, unrelated	Fludarabine, melphalan	ATG, methotrexate, tacrolimus	Yes (gastro-intestinal [delayed], skin)	Yes (skin, 20 m)	Corticosteroids, tacrolimus	Corticosteroids, tacrolimus
11	54	M	ALL	UCBT	Cyclophosphamide, fludarabine, thiotepa, TBI	Cyclosporine (224 d), MMF (35 d)	Yes (gastro-intestinal, liver and skin)	No	Corticosteroids, cyclosporine, MMF	NA
12	45	M	NHL	UCBT	Cyclophosphamide, fludarabine, thiotepa, TBI	Cyclosporine, MMF (45 d)	No	No	NA	NA
13	33	F	HL	PBHCT, related	Fludarabine, melphalan	Cyclosporine, methotrexate, MMF	No	No	NA	NA
14	51	F	HL	UCBT	Cyclophosphamide, fludarabine, thiotepa, TBI	MMF, tacrolimus	Yes (gastro-intestinal)	Yes (skin, 2 m)	Corticosteroids, sirolimus	No

(Continued)

Kidney Medicine

Table 1 (Cont'd). Patients Demographics and aHCT Characteristics

Patient	Age at Biopsy, y	Sex	aHCT Indication	aHCT Type	Conditioning Regimen	GVHD Prophylaxis (Duration if Not Continued as GVHD Treatment[a])	aGVHD (site)	cGVHD (Site, Moment of Appearance Before NKB)	GVHD Treatments Received	GVHD Systemic Treatment at Time of NKB
15	65	F	CLL	PBHCT, related	Fludarabine, melphalan	Cyclosporine (120 d), methotrexate	No	Yes (skin gastro-intestinal and liver, 7 m)	Corticosteroids, cyclosporine, MMF, sirolimus tacrolimus	Corticosteroids, MMF
16	51	F	CML	PBHCT, related	Busulfan, cyclophosphamide	ATG, cyclosporine, methotrexate,	No	Yes (serositis, 2 m)	Corticosteroids, tacrolimus	Corticosteroids
17	44	F	AML	PBHCT, related	Cyclophosphamide, TBI	Cyclosporine, methotrexate	Yes (skin)	Yes (skin and mouth, 8 m),	Corticosteroids, MMF, tacrolimus	MMF, tacrolimus

Abbreviations: aGVHD, acute graft-versus-host disease; aHCT, allogeneic hematopoietic cell transplantation; GVHD, graft-versus-host disease; cGVHD, chronic graft-versus-host disease; NKB, native kidney biopsy; F, female; AML, acute myeloid leukemia; PBHCT, peripheral blood hematopoietic cell transplant; TBI, total body irradiation; ATG, antithyroglobulin antibodies; MMF, mycophenolate mofetil; NA, not applicable; M, male; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; ECP, extracorporeal photopheresis; BMT, bone marrow transplant; HL, Hodgkin's lymphoma; ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; UCBT, umbilical cord blood transplant.

[a]Methotrexate is usually administered as 3 or 4 doses in the first 2 weeks after aHCT and ATG as a single dose, so no duration of treatment was indicated for these drugs. If no duration is written, the drug was continued as GVHD treatment.

but her serum creatinine concentration remained unchanged.

Acute Kidney Injury

Six patients underwent kidney biopsy for AKI, with a median time of 9 months (range, 1-68 months) between their aHCT and kidney biopsy.

The period after aHCT for patient 3 was marked with severe GVHD, unresponsive to multiple therapies, and repeated hospitalizations. More than 5 years after his aHCT, his serum creatinine concentration increased to 2.05 mg/dL. Kidney biopsy showed BK virus nephropathy, TMA, and immune complex nephropathy (Fig 2). The immunosuppressive regimen was reduced. However, the GVHD relapsed and resulted in the patient's death a few weeks later.

Patient 10 visited the emergency department ~3 years after his aHCT because of fatigue and myalgia. A medical history was relevant for nonsteroidal anti-inflammatory drug (NSAID) use the week before. On arrival, his serum creatinine concentration was 9.76 mg/dL, without indication for acute dialysis. On the basis of a presumptive diagnosis of NSAID-induced AIN, glucocorticoids were initiated, and kidney function improved rapidly. A kidney biopsy was performed and confirmed the diagnosis of AIN. In addition, he showed BK viremia with a viral load of 1120 copies/mL, but no viral inclusions were noted on light microscopy and immunohistochemistry study for SV40 showed negative results on kidney biopsy. Glucocorticoids were progressively tapered, and at follow-up 3 months later, the creatinine level reduced to 1.13 mg/dL.

Patient 12 developed AKI and hemorrhagic cystitis with BK and adenovirus viremia and viruria. Considering a persistent fever, he was started on cidofovir and probenecid with intensive intravenous hydration. However, the AKI progressed despite cidofovir treatment. A kidney biopsy demonstrated ATI without viral inclusions (with negative results for SV40 immunohistochemistry). Cidofovir was subsequently stopped, and his serum creatinine level reduced to the baseline value over the next year.

Patient 13 showed a rapid increase in serum creatinine levels 3 months after aHCT, reaching a serum creatinine concentration of 2.17 mg/dL. In the absence of GVHD, calcineurin inhibitor (CNI) was stopped. Given the lack of an obvious AKI etiology, biopsy was requested, which showed ATI with features suggestive of CNI toxicity. Her serum creatinine level subsequently improved but never reached her pretransplantation level, with the last recorded value being 1.35 mg/dL 6 months after AKI (compared with a previous baseline value of 0.79 mg/dL).

Patient 15 developed CKD after aHCT but did not undergo biopsy at that time. Her new baseline creatinine level was ~1.58 mg/dL. However, 12 months after transplantation, her serum creatinine concentration increased suddenly up to 4.22 mg/dL, with a proteinuria of 0.55 g/d. Moreover, kidney biopsy showed features of TMA. She was treated with glucocorticoids, mycophenolate mofetil

Table 2. Kidney Disease Presentation and Pathologic Diagnoses

Patient	Biopsy Indication	Serum Creatinine, mg/dL	eGFR, mL/min/1.73 m²	Proteinuria	Hematuria, RBC/HPF	Biopsy Timing After aHCT, m	Main Pathologic Diagnosis
1	Proteinuria	0.57	>120	2.47 g/d	>20	3	TMA and ATI
2	CKD	2.59	28	0.55 g/d	–	15	TMA and ATI
3	AKI	1.76	42	0.23 g/d	–	68	BK nephropathy, TMA, and immune complex nephropathy
4	NS	0.76	100	3.7 g/d	–	5	MCD
5	NS	0.84	>120	30.77 g/d	6-10	24	MN and FSGS
6	CKD	1.71	42	NA	3-5	21	TMA
7	NS	0.86	93	3.85 g/d	6-10	18	MN and TMA
8	NS	0.85	119	6.82 g/d	>20	25	MN
9	CKD	2.13	30	76 mg/mmol	–	15	TMA
10	AKI	9.76	6	Neg (spot)	–	33	AIN
11	CKD	2.47	29	64 mg/mmol	–	46	TMA
12	AKI	2.05	38	0.88 g/d	>20	1	ATI
13	AKI	1.70	39	0.4 g/d	1-2	3	ATI
14	CKD	1.14	55	343 mg/mmol	–	14	TMA
15	AKI on CKD	4.22	10	0.55 g/d	3-5	11	TMA
16	AKI	1.96	29	1.19 g/d	–	6	ATI and karyomegalic-like interstitial nephritis
17	Proteinuria	1.86	33	3.14 g/d	–	15	MN and TMA

Abbreviations: eGFR, estimated glomerular filtration rate; RBC, red blood cells; HPF, high power field; aHCT, allogeneic hematopoietic cell transplantation; TMA, thrombotic microangiopathy ATI, acute tubular injury; CKD, chronic kidney disease; AKI, acute kidney injury; NS, nephrotic syndrome; MCD, minimal change disease; MN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; AIN, acute interstitial nephritis.
Laboratory values are the most recent before biopsy or the ones that mandate biopsy.

(MMF), and eculizumab. She responded partially to this therapy with her last serum creatinine concentration being 2.40 mg/dL.

Patient 16 underwent a peripheral blood–related aHCT to treat chronic myeloid leukemia refractory to tyrosine kinase inhibitors. She received a myeloablative regimen with busulfan and cyclophosphamide. Her clinical course after aHCT was notable for several AKI episodes: the first one in the context of a sinusoidal obstruction syndrome, and another one presumed to be secondary to foscarnet prescribed for human HSV 6 viremia. Given hemorrhagic cystitis with confirmed BK viruria, a treatment of intravesical cidofovir was initiated. A third AKI episode developed concomitantly to intravesical cidofovir therapy with de novo hyperchloremic metabolic acidosis, hypouricemia, and glucosuria without frank hypokalemia or hypophosphatemia. She was diagnosed with tubular acidosis and started on sodium bicarbonate. She was discharged with a serum creatinine concentration of 1.57 mg/dL. Her serum creatinine level continued to increase (up to 1.96 mg/dL), which mandated the kidney biopsy 6 months after her aHCT.

Kidney biopsy consisted of 2 cores of kidney tissue containing 57 glomeruli, of which 5 were globally sclerotic. Glomeruli were unremarkable. Diffuse ATI was observed, with epithelial thinning, loss of brush border, and epithelial sloughing. Tubular epithelial cells showed marked karyomegaly, characterized by hyperchromatic and increased-sized nuclei showing highly irregular nuclear contours (Fig 3). These nuclear changes were found throughout the nephron, predominating in the proximal tubule. No viral inclusions were noted. Interstitial fibrosis was mild, covering <25% of cortical surface, with mild mononuclear interstitial inflammation, interstitial edema, and few tubulitis lesions. There was mild atherosclerosis and arteriolosclerosis. Immunohistochemistry studies for SV40, cytomegalovirus, adenovirus, Epstein-Barr virus, HSV-1, and HSV-2 showed negative results. Routine immunofluorescence also showed negative results. Electronic microscopy showed enlarged tubular epithelial cells nuclei with convoluted nuclear membranes. A diagnosis of ATI with features of karyomegalic-like interstitial nephritis was made.

The patient began a standard-of-care kidney protection therapy with angiotensin-converting enzyme inhibitors. Her serum creatinine level progressively improved, and the angiotensin-converting enzyme inhibitor was ceased because of low blood pressure. Her serum creatinine concentration has remained stable at 1.64 mg/dL on the last follow-up, 22 months after the diagnosis of AKI.

Nephrotic Syndrome and Proteinuria

A total of 4 patients underwent biopsy because of nephrotic syndrome, and 2 reported significant (non-nephrotic) proteinuria; the median time between transplantation and kidney biopsy being of 17 months (range, 3-25 months). Most of them (n=4) was diagnosed with MN (Fig 4), 1 with MCD, and 1 with ATI. Two patients showed concomitant features of TMA.

Table 3. Pathologic Findings on Kidney Biopsy

	Main Light Microscopy Findings	# GS	TA/IF	ATI	Arteriolo-sclerosis	Routine IF	C4d	PLA2R
1	TMA; glomerular ischemic changes, and glomerular and arteriolar fibrin thrombi	0/18	Mild	Yes	Moderate	Neg	Mesangial (1+)	NA
2	TMA; glomerular ischemic changes, mesangiolysis, GBM duplication, arteriolar intimal edema, and lamination	2/28	Moderate	Yes	Severe	Neg	Linear GBM (1+) Mesangial (1+) Arteriolar (1+)	NA
3	BK virus nephropathy (SV40+), TMA; glomerular ischemic changes, mesangiolysis, GBM duplication, immune complexes GN, and segmental scleroses	12/58	Severe	Yes	Severe	Granular GBM and mesangial IgG (1+), C3 (1+), C1q (2+), κ (1+), λ (1+)	Granular GBM (1+) Mesangial (1+)	NA
4	Normal gloms and FPE 30%	5/25	Mild	No	Moderate	Neg	NA	NA
5	MN, stage 2 and FSGS, tip variant	3/50	Mild	Yes	Mild	Granular GBM IgG (3+), C3 (2+), C1q (1+), κ (2+), λ (2+)	Granular GBM (1+)	Neg
6	TMA; glomerular ischemic changes, mesangiolysis, and GBM duplication	2/22	Moderate	Yes	Severe	Neg	Mesangial (1+) Arteriolar (1+)	NA
7	MN, stage 2, TMA; ischemic changes, glomerular fibrin thrombi, mesangiolysis, and GBM duplication	0/15	Mild	No	Mild	Granular GBM IgG (3+), C3 (+), κ (2+), λ (3+)	Granular GBM (1+)	Neg
8	MN, stage 2 and FSGS NOS	0/14	Mild	No	None	Granular GBM IgG (3+), C3 (1+), κ (2+), λ (2+)	NA	Neg
9	TMA; mesangiolysis, GBM duplication, mesangial expansion and hypercellularity	2/24	Mild	No	Moderate	Neg	Mesangial (1+) Arteriolar (1+)	NA
10	AIN; moderate interstitial infiltrate, edema, and tubulitis	4/33	Mild	Yes	Moderate	Neg	NA	NA
11	TMA; mesangiolysis, fragmented RBC, GBM duplication, mesangial expansion and hypercellularity	18/35	Moderate	No	Moderate	Neg	Mesangial (1+) Arteriolar (1+)	NA
12	ATI	1/11	Mild	Yes	None	Neg	NA	NA
13	ATI with proximal epithelial cell isometric vacuolizations	0/38	Mild	Yes	Mild	Neg	NA	NA
14	TMA; mesangiolysis, GBM duplication	1/10	Moderate	No	Mild	Neg	Mesangial (1+)	NA
15	TMA; mesangiolysis, fragmented RBC, GBM duplication, segmental scleroses, arteriolar intimal edema	3/10	Moderate	No	Severe	Neg	Mesangial (1+) Arteriolar (1+)	NA
16	ATI with features of karyomegalic-like interstitial nephritis	4/57	Mild	Yes	Mild	Neg	NA	NA
17	MN, stage 2, TMA; glomerular ischemic changes, mesangiolysis, GBM duplication, and arteriolar fibrin thrombi	1/22	Moderate	Yes	Mild	Granular GBM IgG (3+), κ (1+), λ (2+)	Granular GBM (1+) Arteriolar (1+)	Neg

Abbreviations: GS, global sclerosis; TA/IF, tubular atrophy/interstitial fibrosis; ATI, acute tubular injury; IF, immunofluorescence; TMA, thrombotic microangiopathy; Neg, negative; NA, non-applicable; GBM, glomerular basement membrane; GN, glomerulonephritis; FPE, foot process effacement; MN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; NOS, not otherwise specified; RBC, red blood cell; AIN, acute interstitial nephritis; Immunofluorescence are described, if positive, on a scale from 1 to 3, 3 being the most intense capture.

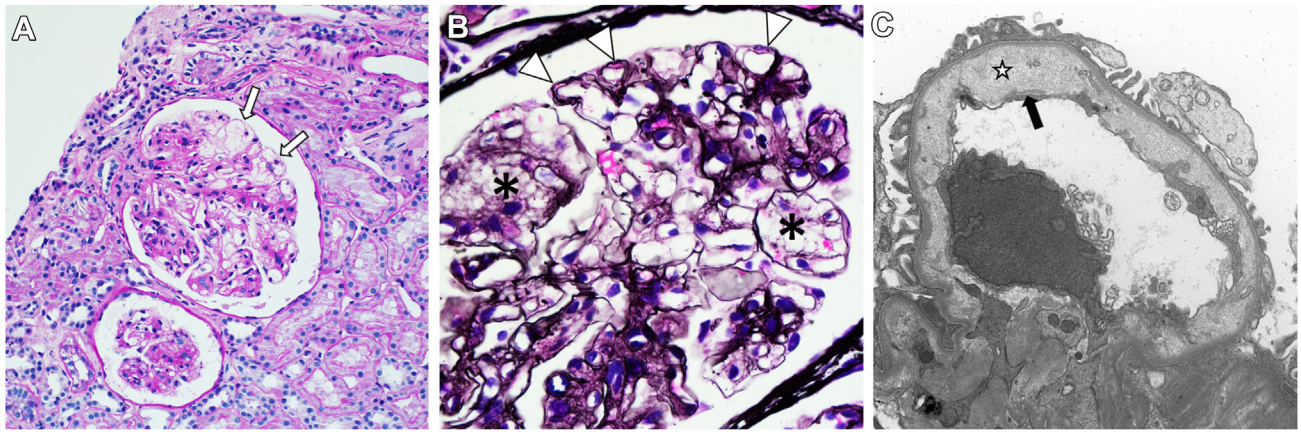

Figure 1. Kidney biopsy findings in patient 9 with thrombotic microangiopathy. (A) On light microscopy, glomeruli show mesangiolysis (white arrows) (periodic acid-Schiff). Original magnification, ×200. (B) At higher magnification, mesangiolysis (asterisks) and duplication of the glomerular basement membrane is present (arrow heads) (Jones silver stain). Original magnification, ×600. (C) On electron microscopy, there is subendothelial space expansion by electron-lucent material (star), with segmental neomembrane formation (black arrow). Original magnification, ×10,000.

Patient 1 did not receive any treatment for her proteinuria because her acute myeloid leukemia relapsed a few weeks after biopsy, and she died 3 months later of neutropenic pneumonia. Of the remaining 5 patients, all but patient 17 were treated with glucocorticoids and CNIs, and patients 4 and 5 also received MMF. Patient 17 was treated with MMF and rituximab and achieved partial remission, with her last 24-hour proteinuria being 0.57 g/d. The remainder of patients reached complete remission. Proteinuria in patient 7 relapsed twice but achieved complete remission with repeated glucocorticoid therapy.

Serum anti-PLA2R antibody was measured in patients 5 and 17 and showed negative results. Immunohistochemistry studies for PLA2R performed on the kidney biopsies with MN showed negative results.

Review of literature

The initial search on PubMed and Embase identified 1,744 articles. Title and abstract of these articles were reviewed, resulting in 49 of them being selected for a more comprehensive analysis. Of these, 9 were excluded because of duplication. Eighteen articles were rejected for not meeting our criteria. Finally, 22 articles were selected. A total of 143 patients were included in this review. A summary of each article is presented in Table 4.[8-28]

DISCUSSION

We report a group of 17 patients who underwent NKB after aHCT given the presence of CKD, AKI, nephrotic syndrome, or significant subnephrotic proteinuria. Pathologic findings

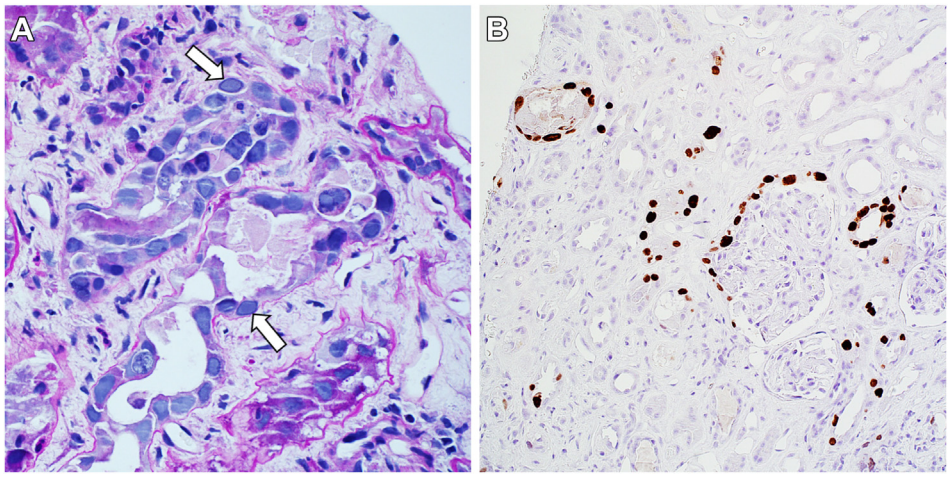

Figure 2. Kidney biopsy findings in patient 3 with BK virus nephritis. (A) Light microscopy shows ground glass intranuclear inclusions in tubular epithelial cells (arrows) (periodic acid-Schiff). Original magnification, ×600. (B) Immunohistochemistry study using antibody for simian virus 40 reveals strong nuclear staining in tubular epithelial cells and parietal epithelial cells. Original magnification, ×200.

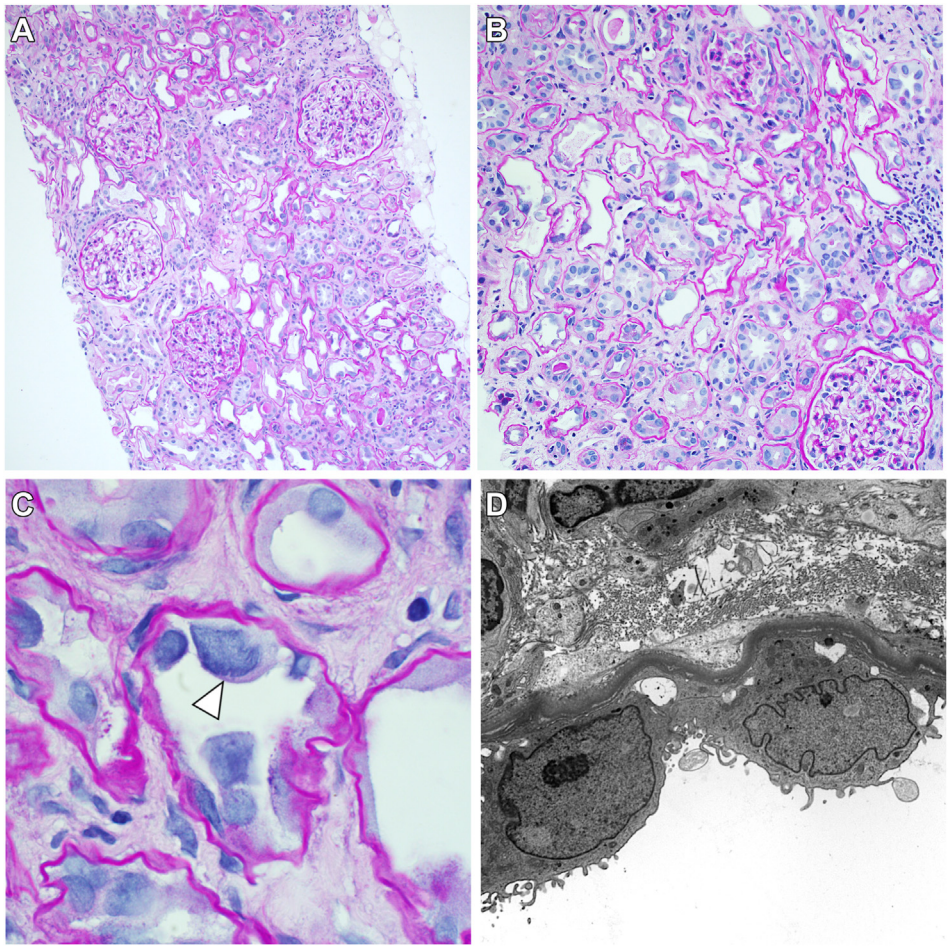

Figure 3. Kidney biopsy findings in patient 16 with acute tubular injury with features of karyomegalic-like interstitial nephritis. (A) Light microscopy shows diffuse acute tubular injury with mild tubular atrophy and interstitial fibrosis (periodic acid-Schiff). Original magnification, ×100. (B) Epithelial thinning, loss of brush border is seen with marked karyomegaly, predominating in proximal tubular epithelial cells (periodic acid-Schiff). Original magnification, ×200. (C) Nuclei are hyperchromatic and increased-sized with highly irregular nuclear contours (arrowhead) (periodic acid-Schiff). Original magnification, ×1,000. (D) Electronic microscopy shows enlarged tubular epithelial cells nuclei with convoluted nuclear membranes. Original magnification, ×5,000.

in patients with CKD were notable for TMA in all patients. Patients experiencing AKI showed more heterogeneous presentations on kidney biopsy: 4 presented with ATI and 2 with TMA, whereas AIN and BK virus nephropathy were noted in 1 patient each. All but 1 patient with nephrotic syndrome were diagnosed with MN. We are also reporting, to our knowledge, the first case of karyomegalic-like interstitial nephritis causing AKI after aHCT.

It is of interest to note that TMA was a common diagnosis in our series and was present in all biopsy indication groups. For most patients with TMA, this diagnosis was not suspected by physicians before kidney biopsy. There are no universally accepted clinical criteria for diagnosis of transplant-associated TMA, but Cho et al[29] validated some criteria based on 2 diagnostic guidelines. Young et al[30] proposed in 2021 criteria based on a review of all those published previously. When evaluating the 10 patients with kidney biopsy-proven TMA using these criteria retrospectively (Table 5), none showed the necessary elements for a clinical diagnosis of TMA, mainly because schistocytes were absent, haptoglobin level was normal for all but 2 patients, and no new-onset or significant worsening of hypertension was noted. These results are similar to those described in a previous study showing a mismatch between blood test results and pathologic kidney findings of transplant-associated TMA at autopsy,[31] suggesting that the present criteria are not sensitive enough to detect kidney-isolated TMA. Most patients presented with histologic features of chronic TMA, although 5 cases showed features of acute TMA, such as glomerular and arteriolar fibrin thrombi. It is important to recognize and treat patients with posttransplant TMA early because their mortality rate is significantly higher than those without TMA, even more so in the presence of proteinuria.[32] Of note, total body irradiation (TBI) tended to increase the risk of TMA in previous studies[33]; this trend seems to be present in our cohort because 6 of the 8 patients who received TBI showed TMA compared with only 4 of the 9 in those who

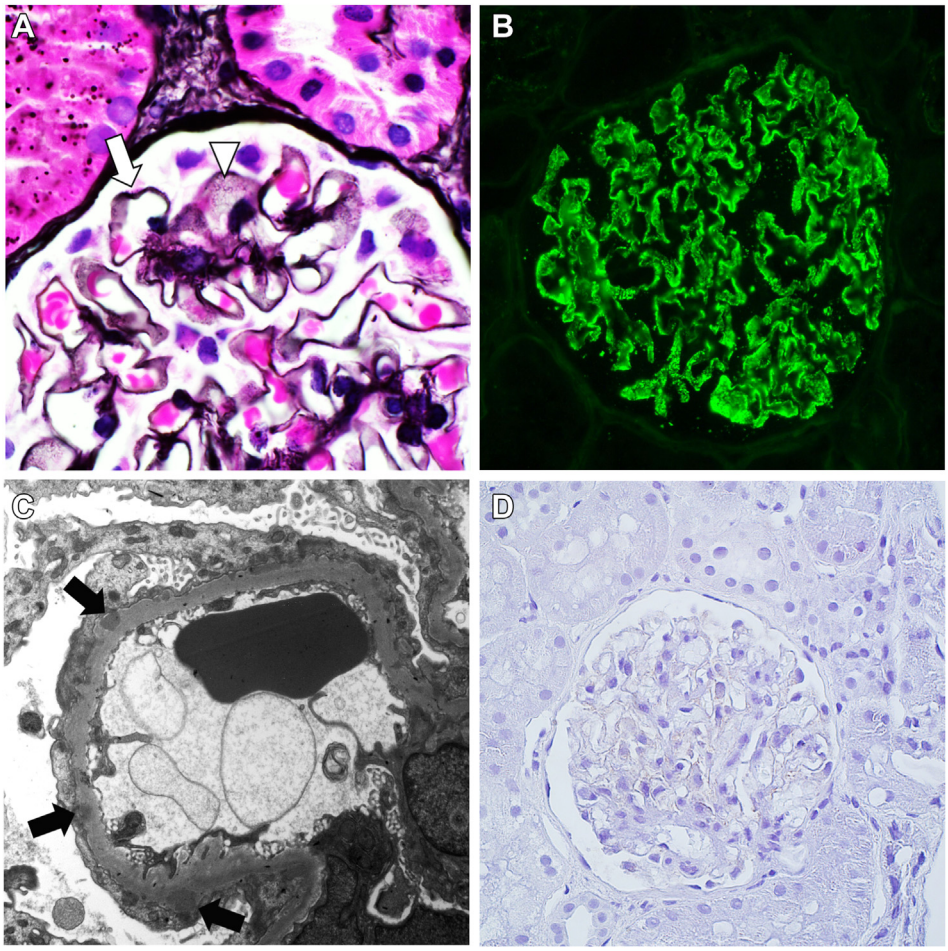

Figure 4. Kidney biopsy findings in patient 8 with membranous nephropathy. (A) On light microscopy, glomerular capillary walls are minimally thickened with subepithelial spikes formation (white arrow) and vacuolated appearance (arrowhead) (Jones silver stain). Original magnification, ×600. (B) Immunofluorescence reveals diffuse granular staining along the glomerular basement membrane for IgG. Original magnification, ×400. (C) On electron microscopy, there are diffuse subepithelial immune-type deposits with diffuse foot process effacement. Original magnification, ×10,000. (D) Immunohistochemistry study for PLA2R is negative. Original magnification, ×400.

did not receive TBI. CNIs and mTOR inhibitors are also recognized as a cause of TMA.[34]

Although no formal criteria have been established for defining kidney GVHD, a growing body of evidence suggests that GVHD might also be associated with intrarenal TMA.[31] Numerous studies found a strong relation between previous GVHD and TMA.[31,35,36] All our 10 patients with TMA also showed a diagnosis of extrarenal acute or chronic GVHD before kidney biopsy, supporting the fact that TMA may represent a kidney expression of GVHD. Patient 3 also showed features of immune complex nephropathy on his kidney biopsy, which could also be a feature suggesting humoral GVHD. C4d deposition has been described as a possible sign of GVHD in skin and colon biopsies[37] and is used in the Banff classification describing kidney transplant rejection.[38] A few studies showed C4d implication with TMA on kidney biopsy, with 1 pediatric study showing arteriolar C4d deposition in hematopoietic stem cell transplantation (autologous and allogeneic) regardless of GVHD,[39] and 1 on adult patients with arteriolar C4d deposition associated with $CD3^+$ T cells infiltration suggestive of GVHD.[40] In our population, no link can be established between C4d deposition pattern and GVHD. Endothelial cells have been shown to be a target of alloreactive T lymphocytes in patients with chronic GVHD.[41] Because endothelial damage is a key step in the pathophysiology of TMA, this might be a plausible biologic explanation linking GVHD and TMA. All these elements tend to suggest that TMA might be a demonstration of kidney GVHD, although a lot of other elements are also demonstrated to trigger TMA in this population.

BK nephropathy is another common cause of kidney disease after kidney transplantation but seems to be less frequent in the aHCT population, in which it causes mainly hemorrhagic cystitis believed to be triggered by the myeloablative regimen's side effects on the urothelial endothelium.[42] A high BK viral load in serum and urine with the presence of BK-associated hemorrhagic cystitis

Table 4. Case Series of Kidney Biopsies After aHCT in the Literature

Reference	Country	N	aHCT Indication	aHCT Type	cGVHD	Biopsy Indication	Biopsy Median Time After aHCT [Max-Min]	Pathologic Diagnosis
Stevenson et al,[8] (2005)	Australia	3	2 AML 1 CML	3 PBHCT	3/3	3 NS	21 [18-24]	2 MN 1 MCD
Srinivasan et al,[9] (2005)	United States	4	3 Nonhematologic causes 1 AML	NA	4/4	4 NS	19 [10-40]	4 MN
Colombo et al,[10] (2006)	Italy	5	2 AML 2 MDS 1 ALL	4 PBHCT 1 UCBT	5/5	5 NS	17 [13-56]	4 MN 1 MCD
Reddy et al,[11] (2006)	United States	6	2 MM 2 MDS 1 CLL 1 ET	6 PBHCT	5/6	6 NS	NA	5 MN 1 MCD
Chang et al,[12] (2007)	United States	11	5 AML 4 MM 1 HL 1 NHL	NA	10/11	5 AKI 5 NS 1 Proteinuria	12 [1-45]	3 MCD 2 TMA 2 MN 2 PVN 1 ATI 1 FSGS
Kemper et al,[13] (2007)	Switzerland	3	2 AML 1 ALL	2 BMT 1 PBHCT	3/3	3 NS	20 [14-21]	2 MN 1 MPGN type 1
Terrier et al,[14] (2007)	France	5	2 NHL 1 AML 1 CLL 1 MDS	NA	5/5	5 NS	21 [14-37]	5 MN
Chan et al[15] (2008)	China	9	4 CML 2 ALL 1 AML 1 MDS 1 MM	NA	7/9	3 NS 3 CKD 3 AKI	34 [1-134]	3 MN 2 TMA 1 IgAN 1 Hypertensive nephrosclerosis 1 ATI 1 MCD
Troxell et al,[16] (2008)	United States	9	4 AML 2 CML 1 NHL 1 MM 1 N/A	6 PBHCT 2 BMT 1 NA	8/9	NA	30 [9-174]	5 MN 1 FSGS 2 ATI and tubulo-interstitial nephritis 1 TMA and CNI-related toxicity
Huang et al,[17] (2012)	China	5	2 AML 2 CML 1 ALL	NA	5/5	5 NS	19 [10-23]	5 MN

(Continued)

Table 4 (Cont'd). Case Series of Kidney Biopsies After aHCT in the Literature

Reference	Country	N	aHCT Indication	aHCT Type	cGVHD	Biopsy Indication	Biopsy Median Time After aHCT [Max-Min]	Pathologic Diagnosis
Cho et al,[18] (2013)	South Korea	15	6 ALL 5 AML 2 CML 1 AA 1 MDS	11 BMT 4 PBHCT	15/15	9 NS 6 Proteinuria	24 [8-144]	12 MN 1 MPGN type 1 1 DN 1 C1q nephropathy
Fraile et al,[19] (2013)	Spain	6	3 AML 1 CML 1 CLL 1 NHL	6 PBHCT	5/6	6 NS	32 [17-45]	4 MN 1 FSGS 1 LN class III
Byrne-Dugan et al,[20] (2014)	United States	4	2 AML 1 ALL 1 MDS	4 PBHCT	2/4	NA	20 [15-60]	4 MN
Chanswangphuwana et al,[21] (2014)	Thailand	3	1 AA 1 CML 1 HL	3 PBHCT	2/3	3 NS	22 [19-24]	2 MN 1 mix of MN, MPGN and LN class III and V
Dhakal et al,[22] (2015)	United States	9	5 AML 2 CLL 1 MM 1 NHL	9 PBHCT	7/9	9 proteinuria	6 [11-84]	4 MN 2 Tubulitis 2 FSGS 1 MCD
Brinkerhoff et al,[23] (2016)	United States	8	3 AML 2 MDS 1 AA 1 ALL 1 NHL	4 BMT 2 PBHCT 2 UCBT	8/8	NA	27 [10-252]	3 TMA 2 MCD 1 FSGS 1 FSGS + DN 1 Anti-GBM nephropathy
Hiramatsu et al,[24] (2016)	Japan	5	3 NHL 1 MDS 1 ALL	5 UCBT	5/5	5 NS	18 [9-40]	4 MN 1 MPGN type 1
Wong et al,[25] 2016	Australia	4	2 AML 1 ALL 1 NHL	NA	4/4	4 NS	17 [8-36]	3 MN 1 MCD
Girsberger et al,[4] (2018)	Germany	12	3 MM 2 ALL 2 AA 1 ALL 1 CLL 1 CML 1 HL 1 nonhematologic cause	NA	8/12	NA	20 [1-103]	4 TMA 3 MN 2 CNI-related toxicity 1 AIN 1 ATI 1 isolated IFTA
Mii et al,[26] (2018)	Japan	4	1 AA 1 AML 1 MDS 1 NHL	1 BMT 3 UCBT	2/4	4 CKD	6 [4-36]	4 TMA

(Continued)

Table 4 (Cont'd). Case Series of Kidney Biopsies After aHCT in the Literature

Reference	Country	N	aHCT Indication	aHCT Type	cGVHD	Biopsy Indication	Biopsy Median Time After aHCT [Max-Min]	Pathologic Diagnosis
Lee et al,[27] (2019)	United States	8	3 AML 1 CML 1 HLH 1 MDS 1 NHL	5 PBHCT 2 UCBT 1 BMT	NA	NA	NA	5 PVN 3 PVN and TMA 1 PVN and MN
Nasr et al,[28] (2021)	United States	5	4 AML 1 ALL	3 PBHCT 1 BMT 1 NA	5/5	3 NS 2 NS + AKI	36 [19-41]	2 MN + TMA + ATI + AIN 2 MN + ATI + AIN 1 MN + TMA

Abbreviations: AA, aplastic anemia; AKI, acute kidney injury; AIN, acute interstitial nephritis; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ATI, acute tubular injury; BMT, bone marrow transplant; cGVHD, chronic graft-versus-host disease; CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; CNI, calcineurin inhibitor; DN, diabetic nephropathy; ET, essential thrombocytosis; FSGS, focal segmental glomerulosclerosis; HCT, hematopoietic cell transplant; LN, lupus nephritis; HL, Hodgkin lymphoma; HLH, hemophagocytic lymphohistiocytosis; IFTA, interstitial fibrosis with tubular atrophy; IgAN, IgA nephropathy; MCD, minimal change disease; MDS, myelodysplastic syndrome; MM, multiple myeloma; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; NA, not available; NHL, non-Hodgkin lymphoma; NS, nephrotic syndrome; PBHCT, peripheral blood hematopoietic cell transplant; PVN, polyomavirus nephropathy; TMA, thrombotic microangiopathy; UCBT, umbilical cord blood transplant.

can be seen without evidence of associated nephropathy. Cidofovir, an antiviral drug, has shown positive results in polyomavirus-induced diseases in some case reports of aHCT patients,[43,44] but no randomized controlled trial has demonstrated a significant benefit. In patients with BK viremia treated with cidofovir, identifying the cause of AKI without a kidney biopsy is challenging because cidofovir may frequently cause severe kidney injury.

One patient with AKI showed evidence of AIN, probably secondary to NSAIDs. No biopsy-proven AIN has been described in the aHCT population to our knowledge. Drug-induced AIN has been described as an immune disease, associated with infiltration of T lymphocytes and macrophages in the kidney in response to drug exposure.[45] In our case, the patient had complete donor chimerism before his AIN episode, meaning that the immune phenomenon must have been of allogeneic nature, therefore reflecting a possible form of drug-induced GVHD.

Brukamp et al[3] showed that 61% of the nephrotic syndrome cases after aHCT were caused by MN whereas MCD was responsible for 22% of the cases. In our 4 patients who presented with nephrotic syndrome, this proportion was respected (3 with MN and 1 with MCD). One other patient showed MN without a complete nephrotic syndrome. Given the current published evidence (based on case reports and series), nephrotic syndrome in the aHCT population seems to represent a manifestation of GVHD; nephrotic syndrome typically emerges in those who had GVHD and is temporally linked to immunosuppressive therapy cessation or dosage reduction.[3,20] All our MN biopsies showed negative results for PLA2R. These results are not surprising considering previous data showing that anti-PLA2R antibodies are rarely positive in this population[17] and the recent discovery of protocatherin FAT1 as a possible antigen for MN in patients who underwent aHCT.[46] Although glucocorticoids alone are generally not efficient in primary MN, the response was excellent in our aHCT population (with 3 patients reaching complete remission), supporting the fact that MN might be secondary to GVHD.

Patient 16 seems to be the first described case of karyomegalic-like interstitial nephritis causing AKI in a post-aHCT individual. Karyomegalic interstitial nephritis is a rare genetic disease with progressive CKD and often associated with respiratory symptoms.[47] We identified 2 possible causative factors that may be related to her clinicopathologic presentation: cidofovir toxicity and cyclophosphamide-induced AKI. Two cases of AKI after topical administration of cidofovir have been published[48] but none after intravesical administration. In our case, intravesical cidofovir was given 3 days before serum creatinine level started to increase. A combination of AKI and Fanconi syndrome associated with cidofovir has also been described.[49] However, cidofovir nephropathy is usually characterized by ATI on kidney biopsy. On contrary, many cases of AKI and Fanconi syndrome with ifosfamide, an alkylating agent similar to cyclophosphamide, have been

Table 5. Presence of Clinical Criteria for Diagnosis of Transplant-Associated TMA in Patients With NKB-Proven TMA

Patients	1[a]	2	3	6	7	9	11	14	15	17
≥2 Schistocytes/HPF	No	No	No	No	No	No	No	No	No	No
LDH >210 U/L	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes
Platelets <50 × 10^9/L or decrease ≥50%	Yes	No	Yes	No	No	Yes	No	No	Yes	No
Hemoglobin <13.4 g/dL for men or <11.8 g/dL for women	Yes	Yes[b]	Yes	No	No	Yes[b]	Yes[b]	Yes[b]	Yes[b]	Yes
Haptoglobin <0.14 g/L	Yes	No	No	NA	NA	No	No	Yes	No	No

Note: Values for increased LDH, and decreased hemoglobin and haptoglobin (>210 U/L) are based on the lower limit of normal established by our laboratory.
Abbreviations: TMA, thrombotic microangiopathy; NKB, native kidney biopsy; HPF, high-field power; LDH, lactate dehydrogenase; NA, not available.
[a]Patient 1 relapsed of her leukemia a few weeks after NKB, rendering it difficult to know if these lab values were attributable to TMA or leukemia.
[b]Value never returned to normal after aHCT.

described in the recent literature.[50-52] Pathologic findings found in ifosfamide-induced AKI have been described as karyomegalic-like interstitial nephropathy in 2 case reports.[53,54] In our patient, although the chronology of AKI and Fanconi syndrome favors more cidofovir as a potential culprit, the pathologic appearance of the kidney injury compares with those described after the administration of an alkylating agent such as ifosfamide.

A dozen of case series of NKB after aHCT have been published. Most published series describe patients with a specific clinical presentation (mainly nephrotic syndrome) or a specific pathology, rendering it difficult to generalize these findings to the whole population of patients who underwent aHCT. Thus, this present series is one among the few that comprise NKBs performed for diverse indications. This case series also presents the largest number of adult aHCT patients with NKB ever published.

The main limitation of this study is the low number of patients, making it difficult to generalize the results to the entire aHCT population, although with the cases being divided in 3 main clinical presentations (AKI, CKD, and nephrotic syndrome and proteinuria). Moreover, kidney biopsy was performed only in a small sample of patients; when looking at partial data from an ongoing study at our institution, between January 1, 2010, and November 15, 2015, AKI was diagnosed in the first 100 days after aHCT in 78 patients and none of them underwent kidney biopsy at that time. This suggests that kidney biopsy is rarely performed in the first 100 days after aHCT, although AKI is relatively frequent.

In conclusion, we present a case series of 17 patients who underwent NKB after aHCT. The causative factors of kidney impairment after aHCT differ from the general population in our series, with a higher incidence of TMA. It seems reasonable to perform kidney biopsy in all patients who underwent aHCT and present with unexplained AKI not resolving with standard care, new-onset CKD, or significant proteinuria. New criteria for kidney-isolated TMA also seem necessary because the current criteria were unable to predict the pathologic findings, resulting in irreversible CKD in some of our patients. Considering the significant effect of CKD on mortality and quality of life, it is quite important to aggressively investigate patients with kidney disease to avoid complicating the already complex post-aHCT follow-up with a treatable pathology. Nonetheless, whether the benefits of performing kidney biopsy more systematically would outweigh the risks in the aHCT population remains to be demonstrated by further studies.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Guillaume Roy, MD, Ilinca Iordachescu, Virginie Royal, MD, Caroline Lamarche, MD, MSc, Imran Ahmad, MD, MSc, Annie-Claire Nadeau-Fredette, MD, MSc, and Louis-Philippe Laurin, MD, MSc

Authors' Affiliations: Division of Nephrology (GR, II, CL, A-CN-F, L-PL), Department of Pathology (VR), and Division of Hematology (IA), Hôpital Maisonneuve-Rosemont, Montreal, Quebec, Canada; Department of Pathology and Cellular Biology (VR), and Department of Medicine (CL, IA, A-CN-F, L-PL), University of Montreal, Montreal, Quebec, Canada.

Address for Correspondence: Louis-Philippe Laurin, MD, MSc, Division of Nephrology, Hôpital Maisonneuve-Rosemont, 5415 Boulevard de l'Assomption, Montreal, Quebec, Canada, H1T 2M4. Email: louis-philippe.laurin@umontreal.ca

Authors' Contributions: Study conception and design : L-PL, CL and IA; data acquisition: GR and II; clinical data analysis/interpretation: GR, II, IA, CL, A-CN-F and L-PL; pathologic data analysis/interpretation: VR; supervision: IA and L-PL. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated, and resolved, including with documentation in the literature if appropriate.

Support: A-CN-F and CL are Fonds de recherche du Québec-Santé Junior 1 Scholars. L-PL is a Fonds de recherche du Québec-Santé Junior 2 Scholar.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Data Sharing: For access to original clinical deidentified data, please contact louis-philippe.laurin@umontreal.ca.

Peer Review: Received October 21, 2022. Evaluated by 2 external peer reviewers, with direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form April 1, 2023.

REFERENCES

1. Hingorani SR, Guthrie K, Batchelder A, et al. Acute renal failure after myeloablative hematopoietic cell transplant: incidence and risk factors. *Kidney Int.* 2005;67(1):272-277.

2. Ando M, Ohashi K, Akiyama H, et al. Chronic kidney disease in long-term survivors of myeloablative allogeneic haematopoietic cell transplantation: prevalence and risk factors. *Nephrol Dial Transplant*. 2010;25(1):278-282.
3. Brukamp K, Doyle AM, Bloom RD, Bunin N, Tomaszewski JE, Cizman B. Nephrotic syndrome after hematopoietic cell transplantation: do glomerular lesions represent renal graft-versus-host disease? *Clin J Am Soc Nephrol*. 2006;1(4):685-694.
4. Girsberger M, Halter JP, Hopfer H, Dickenmann M, Menter T. Kidney pathology after hematologic cell transplantation-a single-center observation study of indication biopsies and autopsies. *Biol Blood Marrow Transplant*. 2018;24(3):571-580.
5. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.
6. Eknoyan G, Lameire N, Eckardt K, Kasiske BJKIS. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. 2012;2:1-138.
7. Levin A, Stevens PE, Bilous RW, et al; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney*. 2013;3(1):1-150.
8. Stevenson WS, Nankivell BJ, Hertzberg MS. Nephrotic syndrome after stem cell transplantation. *Clin Transplant*. 2005;19(1):141-144.
9. Srinivasan R, Balow JE, Sabnis S, et al. Nephrotic syndrome: an under-recognised immune-mediated complication of non-myeloablative allogeneic haematopoietic cell transplantation. *Br J Haematol*. 2005;131(1):74-79.
10. Colombo AA, Rusconi C, Esposito C, et al. Nephrotic syndrome after allogeneic hematopoietic stem cell transplantation as a late complication of chronic graft-versus-host disease. *Transplantation*. 2006;81(8):1087-1092.
11. Reddy P, Johnson K, Uberti JP, et al. Nephrotic syndrome associated with chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2006;38(5):351-357.
12. Chang A, Hingorani S, Kowalewska J, et al. Spectrum of renal pathology in hematopoietic cell transplantation: a series of 20 patients and review of the literature. *Clin J Am Soc Nephrol*. 2007;2(5):1014-1023.
13. Kemper MJ, Güngör T, Halter J, Schanz U, Neuhaus TJ. Favorable long-term outcome of nephrotic syndrome after allogeneic hematopoietic stem cell transplantation. *Clin Nephrol*. 2007;67(1):5-11.
14. Terrier B, Delmas Y, Hummel A, et al. Post-allogeneic haematopoietic stem cell transplantation membranous nephropathy: clinical presentation, outcome and pathogenic aspects. *Nephrol Dial Transplant*. 2007;22(5):1369-1376.
15. Chan GS, Lam MF, Au WY, et al. Clinicopathologic analysis of renal biopsies after haematopoietic stem cell transplantation. *Nephrology (Carlton)*. 2008;13(4):322-330.
16. Troxell ML, Pilapil M, Miklos DB, Higgins JP, Kambham N. Renal pathology in hematopoietic cell transplantation recipients. *Mod Pathol*. 2008;21(4):396-406.
17. Huang X, Qin W, Zhang M, Zheng C, Zeng C, Liu Z. Detection of anti-PLA2R autoantibodies and IgG subclasses in post-allogeneic hematopoietic stem cell transplantation membranous nephropathy. *Am J Med Sci*. 2013;346(1):32-37.
18. Cho YH, Kang SH, Kim Y, et al. De novo glomerulitis associated with graft-versus-host disease after allogeneic hematopoietic stem cell transplantation: A single-center experience. *Kidney Res Clin Pract*. 2013;32(3):121-126.
19. Fraile P, Vazquez L, Caballero D, et al. Chronic graft-versus-host disease of the kidney in patients with allogenic hematopoietic stem cell transplant. *Eur J Haematol*. 2013;91(2):129-134.
20. Byrne-Dugan CJ, Collins AB, Lam AQ, Batal I. Membranous nephropathy as a manifestation of graft-versus-host disease: association with hla antigen typing, phospholipase A2 receptor, and C4d. *Am J Kidney Dis*. 2014;64(6):987-993.
21. Chanswangphuwana C, Townamchai N, Intragumtornchai T, Bunworasate U. Glomerular diseases associated with chronic graft-versus-host disease after allogeneic peripheral blood stem cell transplantation: case reports. *Transplant Proc*. 2014;46(10):3616-3619.
22. Dhakal B, Singavi A, Cohen EP, et al. Chronic GVHD and concurrent new-onset nephrotic syndrome in allogeneic transplant recipients. incidence, pattern and therapeutic outcomes. *Bone Marrow Transplant*. 2015;50(3):449-451.
23. Brinkerhoff BT, Houghton DC, Troxell ML. Renal pathology in hematopoietic cell transplant recipients: a contemporary biopsy, nephrectomy, and autopsy series. *Mod Pathol*. 2016;29(6):637-652.
24. Hiramatsu R, Ubara Y, Sawa N, et al. Clinicopathological analysis of allogeneic hematopoietic stem cell transplantation-related membranous glomerulonephritis. *Hum Pathol*. 2016;50:187-194.
25. Wong E, Lasica M, He SZ, et al. Nephrotic syndrome as a complication of chronic graft-versus-host disease after allogeneic haemopoietic stem cell transplantation. *Intern Med J*. 2016;46(6):737-741.
26. Mii A, Shimizu A, Kaneko T, Nakayama K, Yamaguchi H, Tsuruoka S. Renal thrombotic microangiopathy after hematopoietic stem cell transplantation: involvement of chronic graft-versus-host disease. *Kidney Int Rep*. 2018;3(3):743-747.
27. Lee YJ, Glezerman IG, Tamari R, et al. BK polyoma virus nephropathy in hematopoietic cell transplant recipients. *J Onco-Nephrology*. 2019;3(3):113-123.
28. Nasr SH, Leung N, Said SM, et al. Membranous nephropathy with extensive tubular basement membrane deposits following allogeneic hematopoietic cell transplant: a report of 5 cases. *Am J Kidney Dis*. 2022;79(6):904-908.
29. Cho BS, Yahng SA, Lee SE, et al. Validation of recently proposed consensus criteria for thrombotic microangiopathy after allogeneic hematopoietic stem-cell transplantation. *Transplantation*. 2010;90(8):918-926.
30. Young JA, Pallas CR, Knovich MA. Transplant-associated thrombotic microangiopathy: theoretical considerations and a practical approach to an unrefined diagnosis. *Bone Marrow Transplant*. 2021;56(8):1805-1817.
31. Changsirikulchai S, Myerson D, Guthrie KA, McDonald GB, Alpers CE, Hingorani SR. Renal thrombotic microangiopathy after hematopoietic cell transplant: role of GVHD in pathogenesis. *Clin J Am Soc Nephrol*. 2009;4(2):345-353.
32. Jodele S, Davies SM, Lane A, et al. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. *Blood*. 2014;124(4):645-653.
33. Uderzo C, Bonanomi S, Busca A, et al. Risk factors and severe outcome in thrombotic microangiopathy after allogeneic hematopoietic stem cell transplantation. *Transplantation*. 2006;82(5):638-644.
34. Shayani S, Palmer J, Stiller T, et al. Thrombotic microangiopathy associated with sirolimus level after allogeneic hematopoietic cell transplantation with tacrolimus/sirolimus-based graft-versus-host disease prophylaxis. *Biol Blood Marrow Transplant*. 2013;19(2):298-304.
35. Nakamae H, Yamane T, Hasegawa T, et al. Risk factor analysis for thrombotic microangiopathy after reduced-intensity or

myeloablative allogeneic hematopoietic stem cell transplantation. *Am J Hematol*. 2006;81(7):525-531.
36. Fuge R, Bird JM, Fraser A, et al. The clinical features, risk factors and outcome of thrombotic thrombocytopenic purpura occurring after bone marrow transplantation. *Br J Haematol*. 2001;113(1):58-64.
37. Cherry MA, Parekh H, Yu Z, Lerner M, Selby G, Holter J. The role of complement system in the pathogenesis of graft versus host disease. *Biol Blood Marrow Transplant*. 2011;17(2):S333.
38. Roufosse C, Simmonds N, Clahsen-van Groningen M, et al. A 2018 Reference Guide to the Banff Classification of Renal Allograft Pathology. *Transplantation*. 2018;102(11):1795-1814.
39. Laskin BL, Maisel J, Goebel J, et al. Renal arteriolar C4d deposition: a novel characteristic of hematopoietic stem cell transplantation-associated thrombotic microangiopathy. *Transplantation*. 2013;96(2):217-223.
40. Mii A, Shimizu A, Kaneko T, et al. Renal thrombotic microangiopathy associated with chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Pathol Int*. 2011;61(9):518-527.
41. Biedermann BC, Sahner S, Gregor M, et al. Endothelial injury mediated by cytotoxic T lymphocytes and loss of microvessels in chronic graft versus host disease. *Lancet*. 2002;359(9323):2078-2083.
42. Lamarche C, Orio J, Collette S, et al. BK polyomavirus and the transplanted kidney: immunopathology and therapeutic approaches. *Transplantation*. 2016;100(11):2276-2287.
43. Coomes EA, Wolfe Jacques A, Michelis FV, et al. Efficacy of cidofovir in treatment of BK virus-induced hemorrhagic cystitis in allogeneic hematopoietic cell transplant recipients. *Biol Blood Marrow Transplant*. 2018;24(9):1901-1905.
44. Mehrvar A, Naderi A, Mehrvar N, Nourian M. Successful treatment with intravenous and intravascular cidofovir for BK virus-associated hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: a case report. *Case Rep Oncol*. 2021;14(2):892-895.
45. Praga M, González E. Acute interstitial nephritis. *Kidney Int*. 2010;77(11):956-961.
46. Sethi S, Madden B, Casal Moura M, et al. Hematopoietic stem cell transplant-membranous nephropathy is associated with protocadherin FAT1. *J Am Soc Nephrol*. 2022;33(5):1033-1044.
47. Isnard P, Rabant M, Labaye J, Antignac C, Knebelmann B, Zaidan M. Karyomegalic interstitial nephritis: a case report and review of the literature. 2016;95(20):e3949.
48. Saunders IM, Lahoti A, Chemaly RF, Trevino C, Westmoreland M, Hosing C. Topical cidofovir-induced acute kidney injury in two severely immunocompromised patients with refractory multidrug-resistant herpes simplex virus infections. *J Oncol Pharm Pract*. 2016;22(2):325-331.
49. Kazory A, Singapuri S, Wadhwa A, Ejaz AA. Simultaneous development of Fanconi syndrome and acute renal failure associated with cidofovir. *J Antimicrob Chemother*. 2007;60(1):193-194.
50. Das S, Valencia DN, Fershko A. Partial Fanconi Syndrome Induced by Ifosfamide. *Cureus*. 2019;11(1):e3947.
51. Stöhr W, Paulides M, Bielack S, et al. Ifosfamide-induced nephrotoxicity in 593 sarcoma patients: a report from the Late Effects Surveillance System. *Pediatr Blood Cancer*. 2007;48(4):447-452.
52. Oberlin O, Fawaz O, Rey A, et al. Long-term evaluation of Ifosfamide-related nephrotoxicity in children. *J Clin Oncol*. 2009;27(32):5350-5355.
53. Jayasurya R, Srinivas BH, Ponraj M, Haridasan S, Parameswaran S, Priyamvada PS. Karyomegalic interstitial nephropathy following ifosfamide therapy. *Indian J Nephrol*. 2016;26(4):294-297.
54. McCulloch T, Prayle A, Lunn A, Watson AR. Karyomegalic-like nephropathy, Ewing's sarcoma and ifosfamide therapy. *Pediatr Nephrol*. 2011;26(7):1163-1166.