OPEN

The Evolution of Monoclonal Gammopathy of Undetermined Significance in Kidney Transplant Recipients

Marie-France Gagnon, MD,[1] Héloïse Cardinal, MD, PhD,[2] Jean-Pierre Emond, PhD,[3] Mathieu Latour, MD,[4] and Bernard Lemieux, MD[1]

Background. It is unclear if immunosuppression increases the likelihood of malignant transformation of monoclonal gammopathy of undetermined significance (MGUS) and whether adverse renal outcomes in kidney transplant recipients with MGUS are more frequent. **Methods.** We performed a retrospective cohort study of kidney transplant recipients at the Centre Hospitalier de l'Université de Montréal between 2000 and 2016. **Results.** Among 755 study participants, 13 (1.7%) were found to have MGUS before transplant. Two evolved to smoldering multiple myeloma and 2 presented paraprotein-induced allograft injury from light chain deposition disease. Forty-six patients developed posttransplant MGUS (2.5% 5-y cumulative incidence) of which 1 progressed to multiple myeloma and 1 experienced kidney allograft loss from light chain deposition disease. None of the patients with a malignant transformation or paraprotein-induced renal disease after transplantation had had a systematic workup before transplantation to exclude hematologic malignancies and paraprotein-related kidney injury. Nine posttransplant MGUS (21%) were transient. Multivariable analysis revealed that age at transplant (hazard ratio 1.05 per 1-y increase, 95% confidence intervals, 1.02-1.08) and prior cytomegalovirus infection (hazard ratio 2.22, 95% confidence intervals, 1.07-4.58) were associated with the development of MGUS after transplantation. Of 7 post-transplant lymphoproliferative disorders, none were preceded by MGUS. **Conclusions.** Our results suggest that the identification of MGUS in a transplant candidate should lead to further investigations to exclude a plasma cell neoplasm and monoclonal gammopathy of renal significance before transplantation. MGUS arising after transplantation appears to carry a favorable evolution.

(*Transplantation Direct* 2019;5: e489; doi: 10.1097/TXD.0000000000000937. Published online 19 September, 2019.)

Monoclonal gammopathy of undetermined significance (MGUS) affects 3% of adults >50 years old in the general population,[1] yet a higher prevalence has been described in solid organ transplant recipients.[2] MGUS is a premalignant condition with a risk of progression to a hematologic malignancy of 1% per year.[3] Paraproteins may also induce kidney disease, most commonly through renal deposition of the monoclonal immunoglobulin.[4] Monoclonal gammopathy of renal significance (MGRS) refers to small B clones[4] known to impair renal survival.[4,5]

Although immunosuppression may increase the risk of MGUS progression to neoplasm after kidney transplantation, the magnitude of this increase remains unclear. Studies in the specific setting of kidney transplant immunosuppression have yielded discrepant results. While several cases of progression to plasma cell malignancies have been reported in the past,[6-8] a recent registry-based study found no increased risk of neoplastic transformation.[9] Even though it has been hypothesized that MGUS could specifically evolve into nonplasma cell post-transplant lymphoproliferative disorder (PTLD) in kidney

Received 17 July 2019.

Accepted 4 August 2019.

[1] Division of Hematology-Oncology, Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada.

[2] Division of Nephrology, Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada.

[3] Department of Biochemistry, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada.

[4] Department of Pathology and Cell Biology, Centre Hospitalier de l'Université de Montréal, QC, Canada.

M-F.G. collected the data and participated in research design, in the writing of the paper, in the performance of the research and in data analysis. H.C., J-P.E., and B.L. participated in research design, in the writing of the paper, in the performance of the research, and in data analysis. M.L. participated in pathologic review of cases and and provided histology figures for the manuscript.

The authors declare no funding or conflicts of interest.

Correspondence: Marie-France Gagnon, MD, Division of Hematology-Oncology, Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montreal, 1051 Sanguinet StStreet, Montreal, Quebec, Canada, H2X 3E4. (marie-france.gagnon@umontreal.ca).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000000937

transplant recipients, this association has been described with inconsistent frequency.[7,9-14] Moreover, MGRS also tends to recur in kidney allografts with an associated decrease in graft survival.[15-17]

Given the paucity of data regarding the evolution of MGUS detected before or after transplantation, no formal guidelines exist to guide transplant physicians in the decision to screen for MGUS in the pre and post kidney transplant setting. The aim of this study was to describe the risk factors for MGUS diagnosed before or after kidney transplantation and describe its clinical evolution in terms of progression to malignancy and risk of paraprotein-induced renal disease in the allograft.

MATERIALS AND METHODS

Study Population

We conducted a retrospective cohort study including patients who received a kidney transplantation at the Centre Hospitalier de l'Université de Montréal between January 1, 2000, and January 1, 2016. Transplant recipients were identified through our local electronic Transplant Database. Data were collected by chart review. Patients were included if they had had at least one serum protein electrophoresis (SPEP) after kidney transplantation. Exclusion criteria were <18 years of age at time of transplant, previous solid organ transplantation, no follow-up at our center, multiorgan transplant (liver, lung, pancreas, heart), or a history of any plasma cell malignancy (PCM) before transplantation.

Procedures

There is no systematic protocol concerning the screening for MGUS at our center. Hence, SPEP was performed at the discretion of transplant physicians. The presence of M proteins was evaluated by SPEP/serum free light chain (sFLC) ratio and confirmed with serum immunofixation. Native kidney biopsies are not routinely performed during the pretransplant evaluation but can be requested in the absence of renal atrophy if the cause of kidney disease is unclear and there is clinical suspicion of a disease that could recur on the transplanted kidney. Our standard immunosuppressive protocol includes induction with basiliximab and a maintenance regimen of tacrolimus, mycophenolate mofetil, and corticosteroids. Antithymocyte globulin (ATG) is used as induction in place of basiliximab if the calculated panel reactive antibody is >80% before transplantation, if the recipient is African American, or if there is an elevated risk of delayed graft function. The presence of pre or posttransplant MGUS does not alter our immunosuppression protocol.

Outcomes

The main outcomes were the occurrence of myeloma, PTLD, and MGRS. Multiple myeloma and related plasma cell disorders were defined according to the 2014 International Myeloma Working Group diagnostic criteria.[18] PTLD were defined according to the 2016 revision of the WHO classification of lymphoid neoplasms.[19] The results of bone marrow biopsies, SPEP and serum immunofixation, urine protein electrophoresis, and immunofixation, as well as the levels of urine and sFLCs, were also recorded. The latter test became locally available in 2006. We collected data on patient demographics, induction immunosuppression, CMV and BK virus infections (defined by at least 1 positive viral load (>0 copies/mL) by PCR assays), acute rejection episodes (all types of cell-mediated and antibody-mediated rejections as per the Banff classification in use at the time of the biopsy, including borderline rejections), and death-censored graft survival (defined as a new transplantation or return to dialysis).

Statistical Analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are reported as means ± SD or medians and ranges depending on their distribution. We used Chi-square tests or Fisher exact probability tests to assess for between-group differences in categorical variables and Student *t* tests for independent samples for continuous variables. All statistical tests were two-sided with a significance level of 0.05. We used life table analyses to determine the cumulative incidence of MGUS. We performed a Cox multivariable regression to determine risk factors for MGUS appearance after transplantation. Analyses were performed using SPSS Statistics v24.

Ethical Considerations

The present study was approved by our institution review board (2017-6522, CE 16.013–CA).

RESULTS

Between January 1, 2000, and January 1, 2016, 1009 patients received a kidney transplant at our institution. Of those, 166 patients were excluded based on our predefined criteria (Figure 1), while 88 were not included for absence of SPEP. Our study population therefore consisted of 755 patients. Median posttransplant follow-up was 7.5 years. A pretransplant SPEP was available in 375 patients and the remainder had only posttransplant SPEPs. Among the 375 patients with a pretransplant SPEP, 13 (3.4%) were found to have a paraprotein before transplantation. Thirty-one MGUS appeared de novo after transplantation among the 730 patients who had at least one previously normal SPEP (4.2%). In 13 of these 31 cases of MGUS arising after renal transplantation, no SPEP testing had been performed before transplantation, but a normal SPEP collected posttransplant was available before the identification of the paraprotein. Additionally, twelve MGUS were detected in the posttransplant setting in patients who had no previous SPEP results available. In the latter patients, whether or not MGUS antedated transplantation is uncertain. The 5-year cumulative incidence of posttransplant MGUS was 4% when all cases were considered and 2.5% when patients with no previous SPEP available were excluded. The evolution of patients is illustrated in Figure 2.

Pretransplant MGUS: Prevalence, Risk Factors, and Evolution

Patient characteristics are summarized in Table 1. Thirteen patients had pretransplant MGUS. In this group, mean age at transplantation was 59 years. The paraprotein was detected at a median time of 1.7 years before transplantation. The isotype was IgG in most patients (62%) with a median size of 2.25 g/L. Abnormal serum FLC ratio was present in 4 patients (40%). Thus, 53% had a low risk of neoplastic progression according to established criteria (IgG subtype, size <15 g/L, normal sFLC

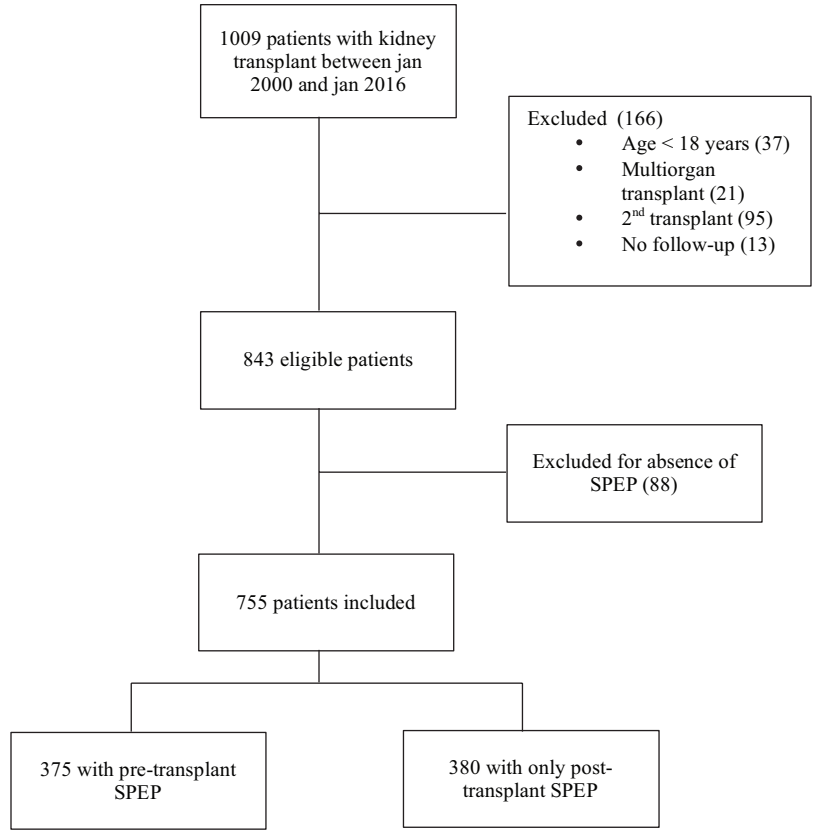

FIGURE 1. Flowchart of the study population with inclusion and exclusion criteria. SPEP, serum protein electrophoresis.

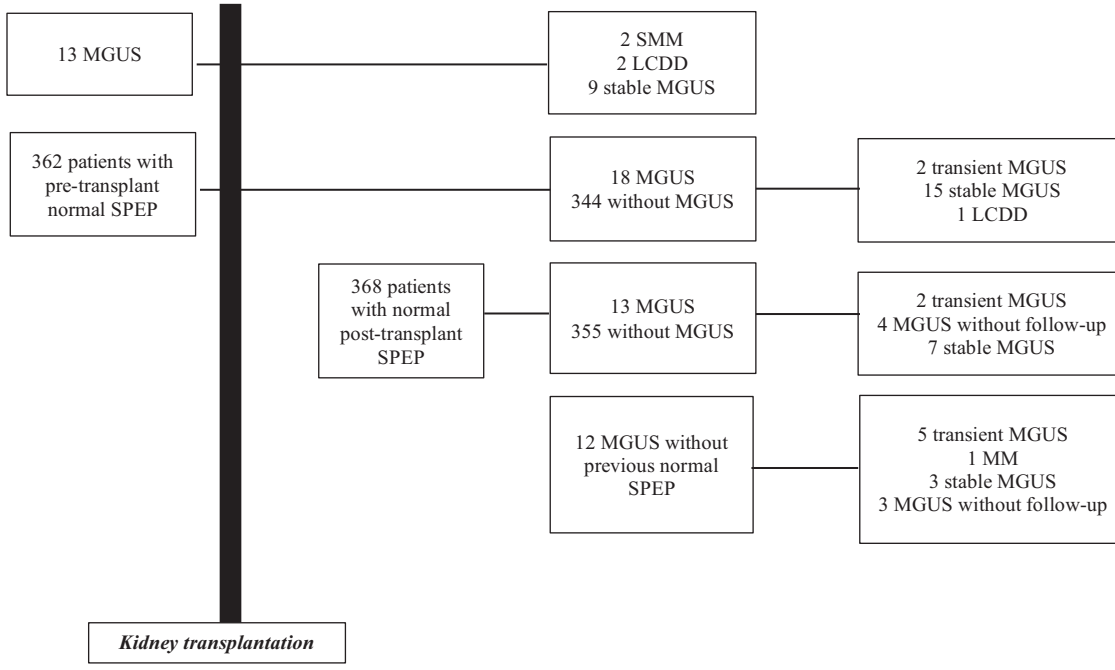

FIGURE 2. Flowchart indicating MGUS status before and after kidney transplantation and the evolution of MGUS in the Study Population. LCDD, light chain deposition disease; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma; SPEP, serum protein electrophoresis.

ratio).[20] Two patients (15%) evolved into smoldering multiple myeloma (SMM) and 2 (15%) demonstrated progressive renal disease from light chain deposition disease (LCDD) after transplantation. Compared with patients with normal SPEP before transplantation (data not shown), patients with pre-transplant MGUS were more likely to be older at the time of transplantation (58.6 versus 49.8 y, *P* value 0.021) and male (92.3% versus 63.1%, *P* value 0.037). We observed no

TABLE 1.

Demographic and clinical characteristics of patients according to MGUS status

	No MGUS (n = 699)	Pretransplant MGUS (n = 13)	Posttransplant MGUS (n = 43)	*P*
Age at transplant, y				<0.001
Mean SD	48.7 (13.2)	58.6 (8.7)	54.7 (12.2)	
Sex (%)				0.068
Male	428 (61)	12 (92)	28 (65)	
Race (%)				0.639
Black	41 (5.7)	1 (7.7)	4 (9.3)	
Cadaveric donor (%)	531 (76)	9 (69)	38 (88)	0.147
Posttransplant follow-up, y				0.014
Mean (SD)	7.8 (6.7)	4.11 (3.1)	8.4 (4.2)	
Underlying kidney disease				0.061
Diabetes	110 (16)	4 (31)	10 (23)	
Polycystic kidney disease	107 (15)	1 (7)	6 (14)	
Hypertensive diseases	26 (4)	0	4 (9)	
Glomerular diseases	254 (36)	7 (53)[a]	7 (16)	
Renal tubulointerstitial diseases	39 (6)	0	6 (14)	
Hereditary	25 (4)	0	1 (2)	
Autoimmune	31 (4)	0	4 (9)	
Congenital	9 (1)	0	1 (2)	
Obstructive	7 (1)	0	1 (2)	
Renal cancer	1 (0.1)	0	0 (0)	
Unknown	58 (8)	1 (7)	1 (2)	
Other	32 (5)	0	2 (5)	
Induction immunosuppression (%)				
Basiliximab	430 (62)	9 (69)	24 (56)	0.636
Tacrolimus	672 (96)	13 (100)	43 (100)	0.326
Mycophenolate mofetyl	673 (96)	13 (100)	40 (93)	0.429
ATG	160 (23)	4 (31)	12 (28)	0.612
Sirolimus	20 (3)	0 (0)	3 (7)	0.256
Transplantation outcomes				
Death-censored allograft loss (%)	78 (11)	0 (0)	8 (19)	0.140
No. kidney transplants (>1) (%)	30 (4.3)	0 (0)	2 (4.7)	0.744
Acute rejection (%)	187 (27)	2 (23.08)	11 (26)	0.951
CMV infection (%)	87 (12)	2 (15.38)	11 (26)	0.057
BK infection (%)	99 (14)	4 (30.77)	11 (26)	0.123
Moment of paraprotein detection before transplant, y				
Median		1.7		
Range		0.2–8.9		
Posttransplant time to paraprotein appearance, y				
Median			3.2	
Range			0.2–14.5	
Paraprotein isotype (%)				0.576
G		8 (62)	32 (74)	
A		1 (8)	5 (12)	
M		2 (15)	2 (5)	
Light chain		1 (8)	2 (5)	
Biclonal		1 (8)	2 (5)	
Size of paraprotein (g/L)				0.551
Median[b]		2.3	0.76	
Range		0.1–8.9	0.1–21.6	
Abnormal sFLC ratio[c] (%)		4 (40)	6 (15)	0.196
Bone marrow biopsy and aspiration performed for MGUS (%)		3 (23%)[d]	12 (28)	0.082
Hematologic outcomes (%)				
SMM	0 (0)	2 (15)	0 (0)	
Multiple myeloma	0 (0)	0 (0)	1 (2)	
Stability	0 (0%)	11 (85%)	33 (76%)	
Disappearance	0 (0%)	0 (0%)	9 (21%)	
PTLD		0 (0%)	0 (0%)	
Paraprotein-induced renal disease in the allograft (%)				
Light-chain deposition disease		2 (15%)	1 (2)	

[a]Of the patients with pretransplant MGUS, only one had potentially paraprotein-induced renal disease (see Table 4).
[b]Missing data for 1 patient with pretransplant MGUS and 7 patients with post transplant MGUS.
[c]Missing data for 3 patients with pretransplant MGUS and 4 patients with post transplant MGUS.
[d]Only bone marrow biopsies and aspirations performed before renal transplantation were considered.
ATG, antithymocyte globulin; MGUS, monoclonal gammopathy of undetermined significance; PTLD, posttransplant lymphoproliferative disorder; SD, standard deviation; sFLC, serum free light chain; SMM, smoldering multiple myeloma.

difference in death-censored allograft survival, acute rejection episodes, and CMV and BK virus infections between patients with normal SPEP and MGUS before transplantation.

Posttransplant MGUS: Incidence, Risk Factors, and Evolution

Forty-three patients were found to have MGUS after transplantation. The paraproteins appeared after a median of 3.2 years. Most (74%) were of IgG isotype. They were characterized by a small median size (0.76 g/L) and sFLC was abnormal in 6 patients (14%). One patient progressed to MM and one was diagnosed with LCDD. The monoclonal component remained stable in 32 patients whereas it was transient in 9 patients (21%). Median time to disappearance was 2.0 years. We could not detect any statistically significant difference between transient and permanent MGUS (Table 2). However, IgG-isotype was identified in 100% of cases in the transient and 67% of cases in permanent MGUS group, and the size of the gammopathy was 0.43g/L in transient versus 2.85 g/L in permanent MGUS. No patients with transient monoclonal gammopathy had an abnormal sFLC ratio compared with 22% of patients with permanent MGUS.

Death-censored allograft survival did not differ between patients who developed MGUS posttransplant and patients without MGUS. The proportion of patients who had potentially paraprotein-related native kidney disease was low and similar in patients who developed MGUS (2%) and those who did not (4%). After adjustment for sex, race, use of ATG, acute rejection episodes and BK virus infection, age at transplantation (hazard ratio 1.05 per 1-y increase; 95% confidence intervals [CI], 1.02-1.08; *P* value 0.001) and CMV infections (hazard ratio 2.22; 95% CI, 1.07-4.58; *P* value 0.031) were associated with the development of posttransplant MGUS (Table 3). Similar results were found when patients with no previously available normal SPEP were excluded.

Progression to Hematologic Malignancies and Appearance of Paraprotein-Induced Renal Disease

Among the 56 transplant recipients with MGUS, 3 patients experienced hematologic progression and 3 developed allograft dysfunction/loss due to MGRS (Table 4). The paraprotein was identified before transplant in 4 patients and after transplant in 2 patients. Among the patients who had hematologic progression of MGUS, 2 presented with SMM and 1 developed MM. The 2 patients who were diagnosed with SMM after transplant had pretransplant MGUS. However, as pretransplant workup did not include a recent bone marrow biopsy, it remains possible that SMM was present yet undetected before transplantation. The patient who was diagnosed with MM did not have an SPEP before transplantation. However, 1 year after transplantation, a 26 g/L IgG-lambda gammopathy was identified which later evolved into MM. Further information describing the 6 patients were hematologic progression and development of MGRS are available as supplemental digital content. Of note, we observed no MGUS progression to nonplasma cell PTLD. We identified 7 cases of non plasma-cell PTLD in our cohort, but none of those were found to have a prior MGUS.

Three patients demonstrated renal insufficiency from LCDD after transplantation. As native pretransplant kidney biopsy for these patients did not include immunofluorescence staining for kappa-lambda light chains and/or paraffin immunofluorescence after pronase digestion when appropriate, we cannot exclude that MGRS may have already been present before transplantation. Figure 3 illustrates the histologic findings of 1 of the 3 patients with allograft dysfunction due to LCDD.

TABLE 2.

Comparison of transient and permanent posttransplant MGUS

	Transient MGUS (n = 9)	Permanent MGUS (n = 27)	*P*
Age at transplant, y; mean (SD)	54.0 (13.2)	55.0 (12.8)	0.006
Sex (%) Males	6 (67)	17 (63)	1.00
Cadaveric donor (%)	7 (78)	24 (89)	0.581
Posttransplant time to appearance, y			0.448
Mean (SD)	3.5 (3.8)	4.8 (4.1)	
Median (IQR)	1.2 (6.4)	2.9 (7.0)	
Posttransplant time to disappearance, y	2.0 (0.3–5.7)		
Median (range)			
Paraprotein isotype (%)			0.191
G	9 (100)	18 (67)	
A	0 (0)	4 (15)	
M	0 (0)	2 (7)	
Light chain	0 (0)	2 (7)	
Biclonal	0 (0)	1 (4)	
Paraprotein size (g/L)			
Mean[a] (SD)	0.43 (0.26)	2.85 (4.88)	0.194
Median[a] (range)	0.45 (0.10–0.80)	0.90 (0.10–21.60)	
Abnormal sFLC ratio[b] (%)	0 (0)	6 (22)	0.299
CMV infection	3 (33)	5 (18)	0.33
BK infection	3 (33)	7 (26)	0.69

Seven patients with no follow-up SPEP were excluded from this table.
[a]Missing data for 3 patients.
[b]Missing data for 2 patients.
IQR, interquartile range; MGUS, monoclonal gammopathy of undetermined significance; SD, standard deviation; sFLC, serum free light chain; SPEP, one serum protein electrophoresis.

TABLE 3.

Risk factors for posttransplant MGUS appearance

	Univariate hazard ratio	95% CI	*P*	Multivariate hazard ratio	95% CI	*P*
Age at transplant	2.92	1.97-10.06	0.003	1.05	1.02-1.08	0.001
Race Black	2.20	0.78-6.17	0.107	1.74	0.58-5.19	0.321
Induction immunosuppression						
ATG	1.62	0.83-3.17	0.449	1.17	0.58-2.39	0.659
Transplant outcomes						
Acute rejection	0.54	0.24-1.21	0.866	0.59	0.26-1.34	0.210
CMV infection	2.26	1.11-4.60	0.014	2.22	1.07-4.58	0.031
BK reactivation	1.25	0.52-2.96	0.041	1.09	0.45-2.61	0.321
Sex male	1.271	0.679-2.380	0.611			
Donor characteristics						
Cadaveric	1.63	0.64-4.15	0.064			
Age	1.01	0.99-1.04	0.422			
Male sex[a]	0.96	0.46-1.97	0.351			

[a]Missing data for 9 patients (8 without MGUS).
ATG, antithymocyte globulin; CI, confidence intervals; MGUS, monoclonal gammopathy of undetermined significance.

TABLE 4.

Description of patients with MGUS undergoing transformation to a plasma cell malignancy

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
	56 y (M)	62 y (M)	40 y (M)	59 y (M)	42 y (F)	62 y (M)
Native kidney disease[a]	FSGS	FSGS	Type 1 MPGN	IgA nephropathy	Nonspecific GN	Malignant HTN
MGUS diagnosis	Pretransplant	Pretransplant	Pretransplant	Pretransplant	Posttransplant[b]	Posttransplant
MGUS type	IgG-lambda	Kappa light chain	IgG-kappa	IgA-lambda	Kappa light chain	IgG-lambda
Initial MGUS size	9.3 g/L	Kappa light chain 1140 mg/L (sFLC ratio 65)	5 g/L	9.3 g/L	Kappa light chain 1927 mg/L (sFLC ratio 64)	26 g/L
Pretransplant BMB	None	None	None	3% clonal plasmocytosis	None	None
Posttransplant time to diagnosis	1 mo	1.23 y	2.5 y	4.67 y	2 mo[c]	8.39 y
Diagnosis	SMM	LCDD	LCDD	SMM	LCDD	MM
Treatment	Observation	CyBorD from 2016/09 to 2016/12 (interrupted for toxicity) with VGPR	CyBorD for 1 y with PR	Observation	CyBorD (5 cycles) followed by ASCT for possible new kidney transplant	VMP (9 cycles) up to 2010, CyBorD in 2014 (6 cycles)
Outcome	Alive	Alive	Alive	Alive	Alive	Dead
Allograft outcome	Functional	Dysfunctional	Dysfunctional	Functional	Loss	Dysfunctional
Posttransplant follow-up	1.78 y	2.07 y	3.97 y	5.47 y	9.52 y	15.33 y

[a]Native kidney disease as per biopsy results from their referring center.
[b]No sFLC pretransplant.
[c]LCDD was officially recognize 8.41 y after transplant. However, an allograft biopsy performed 2 mo posttransplant was retrospectively reviewed at our center and LCDD was diagnosed, confirming the presence of this condition 2 mo posttransplant.
ASCT, autologous stem cell transplantation; BMB, bone marrow biopsy; CyBorD, cyclophosphamide-bortezomib-dexamethasone; FSGS, focal segmental glomerular sclerosis; GN, glomerulonephritis; HTN, hypertension; LCDD, light chain deposition disease; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MPGN, membranoproliferative glomerulonephritis; PR, partial response; sFLC, serum free light chain; SMM, smoldering multiple myeloma; VGPR, very good partial response; VMP, velcade-melphalan-prednisone.

DISCUSSION

In this study, we found a prevalence of MGUS of 3.4% before kidney transplantation and a 2.5% cumulative incidence of MGUS at 5 years after transplant. Among a total of 56 patients with a pre or posttransplant monoclonal gammopathy, 3 experienced hematologic progression to MM or SMM and 3 suffered from paraprotein-induced renal damage (LCDD). However, as pretransplant workup was incomplete, it remains possible that these were already present yet undiagnosed before transplantation. A significant proportion of MGUS appearing after transplant were transient. Our results suggest that older age at transplantation and prior CMV infection may be risk factors for MGUS appearance in kidney transplant recipients.

Previous investigators have described an increased frequency of MGUS in solid organ transplant recipients. Cumulative 5-year incidence rates of 22.5% and 30% have been reported in kidney[11] and heart transplant recipients.[12] In our study population, the incidence of MGUS was lower with an estimated 5-year cumulative incidence of MGUS development of 4% when all posttransplant MGUS were considered and 2.5% when omitting patients for whom posttransplant appearance could not be ascertained. This may reflect variations in immunosuppression protocols as an increased risk of MGUS has been previously described with OKT3 and cyclosporine.[12,21] In

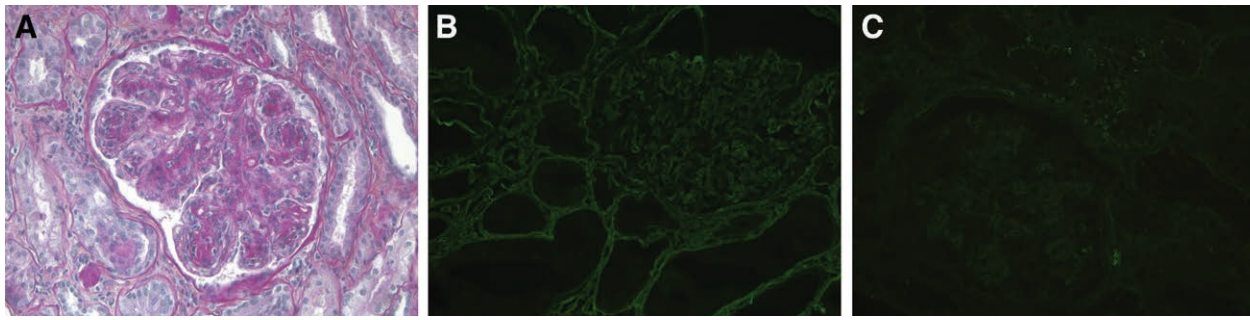

FIGURE 3. Histopathology of monoclonal immunoglobulin deposition disease (MIDD). A, Periodic acid-Schiff (PAS) staining showing strong PAS positivity of MIDD deposits with glomerular sclerosis and mesangial hypercellarity. Thickening of the basement membranes is also demonstrated (magnification ×200). Immunoflurescence in MIDD showing diffuse linear staining of all basement membranes in the kidney with kappa (B) but no significant staining for lambda (C) (magnification ×200).

Caforio's report, in which all patients received cyclosporine, 5-year cumulative MGUS incidence after heart transplant was 21%.[12] Passweg et al[21] found that the risk of developing a gammopathy was 24% if OKT3 was included to induction immunosuppression as compared with 10.4% with ATG. In our study, 2.6% of patients received cyclosporine and OKT3 was never used as induction immunosuppression or rejection treatment. These agents may impair immune surveillance through inhibition of T-cell function, allowing B-cell lineage proliferation.[12] Most of our patients were induced with basiliximab, which has not been linked to an increased probability of paraprotein.[22] Population characteristics such as age and race may also create disparities in MGUS incidence in different reports. Lastly, we may underestimate the incidence of MGUS in our population as a protocol for serial monitoring of SPEP/IFX and sFLC after transplantation was not implemented as compared with some other studies.[21,22]

Thirteen patients with MGUS received a kidney transplant in our population. These patients were found to be older at transplantation with a higher male proportion compared with other transplant candidates. This is consistent with previously described risk factors for MGUS.[2] Among the patients with pretransplant MGUS, 2 (15%) progressed to SMM and 2 (15%) demonstrated LCDD.[23] We cannot exclude that the patients with SMM could have had increased bone marrow clonal plasmocytosis before transplant, as bone marrow biopsy was not performed in 1 patient while it had been done 6 years before transplantation in the other. The native kidney disease of the 2 patients who were diagnosed with posttransplant LCDD may have been linked to a paraprotein. The native kidney biopsy for these 2 patients had been analyzed at their referring center and had not been reviewed by our transplant center before proceeding to transplantation. However, later revision of these specimens showed that immunofluorescence staining for kappa/lambda light chains had not been performed for 1 case. In the other case, a paraffin immunofluorescence after pronase digestion study had not been completed despite a membranoproliferative pattern on light microscopy with predominant C3 deposits on immunofluorescence. In patients with pretransplant MGUS, previous studies report rates of progression to PCM that fluctuate between 0%[13] and 40%.[6] The extent of the pretransplant workup done to exclude MM or MGRS before transplantation in patients with MGUS in these studies was variable, which may explain the variability in progression to malignancy and appearance of paraprotein-induced allograft disease in this patient population.[6-8,13]

Our findings thus point to the importance of a complete evaluation to exclude hematologic malignancies and MGRS in patients with MGUS before transplantation, including the revision of native kidney pathological specimens. SMM carries a 51% cumulative probability of progression to overt malignancy over 5 years in contrast to a 4% probability in the setting of MGUS.[24] Consequently, identification of SMM in a transplant candidate may influence the decision to proceed with transplantation. Alternatively, MGRS tends to recur after transplant and negatively affect allograft survival times.[4,16,25] It is suggested that in the setting of an M-protein and kidney failure, the possibility of causality between these conditions should be investigated.[26] Therefore, it appears important to identify it in transplant candidates. Although MGRS may not be curable, its reappearance in the allograft could be minimized by achieving a complete hematologic response.[27]

Previous literature has suggested a relatively benign course of posttransplant MGUS. In a report of 46 posttransplant MGUS among 390 kidney transplant recipients, none evolved to a hematologic malignancy after a median follow-up of 1 year.[21] In another study of 45 posttransplant MGUS among 203 kidney transplant patients followed for >5 years, none experienced malignant transformation.[11] In our study, among 43 MGUS diagnosed after transplant, 1 patient developed LCDD in the allograft and another evolved into MM. In the former, native kidney biopsy immunofluorescence did not include staining for kappa and lambda light chains. Two months after transplant, LCDD was identified in her kidney graft. Given this short lapse of time, it seems plausible that this condition may have existed before transplant and contributed to initial kidney failure. In the second patient who developed MM after transplant, no SPEP was performed before transplant, yet 1 year later, he was diagnosed with an MGUS of significant size (26 g/L). He later progressed to overt MM. It appears likely that MGUS was already present before transplant in this patient. Taken together, our results suggest that malignant evolution of MGUS in the setting of renal transplantation is low and may be similar to that of the general population as the cases of PCMs we observed may have already been present before transplantation.

A significant proportion of posttransplant MGUS were transient (21%). Although spontaneous disappearance of MGUS is relatively uncommon in the general population with a frequency of 2%,[3,28] this phenomenon has been described in several solid organ transplant series with MGUS being transient in up to 37%–72% of patients.[11,21,29,30] MGUS arising after transplant may thus have a different pathophysiology.

Previous studies have identified an association between CMV infection and MGUS appearance.[10,11,30,31] It has been hypothesized that CMV could induce paraprotein appearance through polyclonal B-cell activation.[31] Our findings support this association. In contrast, in a recent retrospective report of 39 posttransplant MGUS, CMV infections did not correlate with paraprotein appearance. This discrepancy could be explained by the fact that transient MGUS were excluded[22] while we considered both transient and permanent cases.

Previous studies have suggested a possible link between MGUS and the risk of nonplasma cell PTLD.[7,10,12] In our cohort, none of the 7 cases of PTLD were preceded by MGUS, which is consistent with results from a larger recent study in which no PTLD developed over 6 years among 72 patients with pretransplant MGUS.[9]

Our study has some limitations. Current clinical practice guidelines do not provide any recommendation for or against screening for MGUS before[32] or after kidney transplantation.[33] Hence, SPEP was performed at the discretion of transplant physicians. Because of its retrospective nature, SPEP, immunofixation, urine immunoelectrophersis, and sFLC ratio were not available before and/or after transplant for all patients and some recipients were lost to follow-up, which may underestimate the true incidence of MGUS. There was missing data related to sFLC as this test only became available at our institution in 2006. Moreover, screening for a gammopathy was performed with SPEP and immunofixation was only added to confirm or exclude the presence of a paraprotein in the setting of a SPEP anomaly. This may have underestimated the prevalence of gammapathy as SPEP is less sensitive then immonofixation for the detection of paraprotein. Given a relatively limited sample size and associated wide CI, we cannot rule out that recipient race, BK virus infections and induction immunosuppression with ATG could increase the risk of MGUS. Finally, median follow-up after transplant was limited to 7.5 years. With longer follow-up, it is possible that additional patients with MGUS may progress to PCMs.

CONCLUSION

In conclusion, we found a prevalence of MGUS of 3.4% before transplantation, which is consistent with data obtained from the general population.[1] Although this figure is low, we suggest that a complete workup (with SPEP, UPEP, and sFLC with serum and urine immunofixation) to identify a monoclonal gammopathy be performed before transplantation as this could lead to changes in the management of a transplant candidate. If a paraprotein is found, a PCM or MGRS should be excluded before transplantation. In this respect, we suggest that a bone marrow biopsy as well as a careful revision of the native kidney biopsy be performed before transplantation. The presence of SMM/MM may change the decision to proceed with transplantation, while treatment for MGRS may prevent or delay recurrent disease in the allograft. The evolution of MGUS arising in the post transplant setting seems similar to that of the general population, and a significant proportion appear to be transient. Hence, our results do not support changes in the management of MGUS in kidney transplant recipients compared with that of the general population. Consequently, we do not recommend routine screening for MGUS after renal transplantation and SPEP/IFX/sFLC should be performed when clinically indicated.

ACKNOWLEDGMENTS

The authors thank Dr Alexandra Laforest-Renald for providing additional data pertaining to certain patients included in this study.

REFERENCES

1. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2006;354:1362–1369.
2. Wadhera RK, Rajkumar SV. Prevalence of monoclonal gammopathy of undetermined significance: a systematic review. *Mayo Clin Proc.* 2010;85:933–942.
3. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2002;346:564–569.
4. Leung N, Bridoux F, Hutchison CA, et al; International Kidney and Monoclonal Gammopathy Research Group. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. *Blood.* 2012;120:4292–4295.
5. Nasr SH, Valeri AM, Cornell LD, et al. Renal monoclonal immunoglobulin deposition disease: a report of 64 patients from a single institution. *Clin J Am Soc Nephrol.* 2012;7:231–239.
6. Rostaing L, Modesto A, Abbal M, et al. Long-term follow-up of monoclonal gammopathy of undetermined significance in transplant patients. *Am J Nephrol.* 1994;14:187–191.
7. Naina HV, Harris S, Dispenzieri A, et al. Long-term follow-up of patients with monoclonal gammopathy of undetermined significance after kidney transplantation. *Am J Nephrol.* 2012;35:365–371.
8. Redfield RR, Naji A. Progression of monoclonal gammopathy of undetermined significance to multiple myeloma in a solid organ transplant. *Transplantation.* 2011;92:e65–6; author reply e66.
9. Goebel TE, Schiltz NK, Woodside KJ, et al. Neoplastic and non-neoplastic complications of solid organ transplantation in patients with preexisting monoclonal gammopathy of undetermined significance. *Clin Transplant.* 2015;29:851–857.
10. Badley AD, Portela DF, Patel R, et al. Development of monoclonal gammopathy precedes the development of Epstein-Barr virus-induced posttransplant lymphoproliferative disorder. *Liver Transpl Surg.* 1996;2:375–382.
11. Regamey N, Hess V, Passweg J, et al. Infection with human herpesvirus 8 and transplant-associated gammopathy. *Transplantation.* 2004;77:1551–1554.
12. Caforio AL, Gambino A, Belloni Fortina A, et al. Monoclonal gammopathy in heart transplantation: risk factor analysis and relevance of immunosuppressive load. *Transplant Proc.* 2001;33:1583–1584.
13. Jimenez-Zepeda VH, Heilman RL, Engel RA, et al. Monoclonal gammopathy of undetermined significance does not affect outcomes in patients undergoing solid organ transplants. *Transplantation.* 2011;92:570–574.
14. Lemoine A, Pham P, Azoulay D, et al. Detection of gammopathy by serum protein electrophoresis for predicting and managing therapy of lymphoproliferative disorder in 911 recipients of liver transplants. *Blood.* 2001;98:1332–1338.
15. Czarnecki PG, Lager DJ, Leung N, et al. Long-term outcome of kidney transplantation in patients with fibrillary glomerulonephritis or monoclonal gammopathy with fibrillary deposits. *Kidney Int.* 2009;75:420–427.
16. Nasr SH, Sethi S, Cornell LD, et al. Proliferative glomerulonephritis with monoclonal IgG deposits recurs in the allograft. *Clin J Am Soc Nephrol.* 2011;6:122–132.
17. Leung N, Lager DJ, Gertz MA, et al. Long-term outcome of renal transplantation in light-chain deposition disease. *Am J Kidney Dis.* 2004;43:147–153.
18. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15:e538–e548.
19. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127:2375–2390.
20. Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood.* 2005;106:812–817.

21. Passweg J, Thiel G, Bock HA. Monoclonal gammopathy after intense induction immunosuppression in renal transplant patients. *Nephrol Dial Transplant.* 1996;11:2461–2465.
22. Alfano G, Fontana F, Colaci E, et al. Monoclonal gammopathy of undetermined significance after kidney transplantation: single-center experience. *Transplantation.* 2017;101:e337–e342.
23. Bancu I, Cañas L, Juega FJ, et al. Outcomes of monoclonal gammopathy of undetermined significance in patients who underwent kidney transplantation. *Transplant Proc.* 2015;47:2344–2345.
24. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med.* 2007;356:2582-2590.
25. Nambirajan A, Bhowmik D, Singh G, et al. Monoclonal gammopathy of renal significance with light-chain deposition disease diagnosed postrenal transplant: a diagnostic and therapeutic challenge. *Transpl Int.* 2015;28:375–379.
26. Bladé J, Cibeira MT. M-protein-related disorders: MGCS. *Blood.* 2018;132:1464–1465.
27. Fermand JP, Bridoux F, Kyle RA, et al; International Kidney and Monoclonal Gammopathy Research Group. How I treat monoclonal gammopathy of renal significance (MGRS). *Blood.* 2013;122:3583–3590.
28. Kyle RA, Larson DR, Therneau TM, et al. Long-term follow-up of monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2018;378:241–249.
29. Galioto A, Morando F, Rosi S, et al. Monoclonal gammopathy after liver transplantation: a risk factor for long-term medical complications other than malignancies. *Transpl Int.* 2012;25:25–33.
30. Chakalarovski C, Lang P, Buisson C, et al. Monoclonal immunoglobulins in patients with renal transplants: characterization, evolution and risk factors. *Transpl Int.* 1992;5(Suppl 1):S23–S25.
31. Ginevri F, Nocera A, Bonato L, et al. Cytomegalovirus infection is a trigger for monoclonal immunoglobulins in paediatric kidney transplant recipients. *Transplant Proc.* 1998;30:2079–2082.
32. Acuna SA, Huang JW, Scott AL, et al. Cancer screening recommendations for solid organ transplant recipients: a systematic review of clinical practice guidelines. *Am J Transplant.* 2017;17:103–114.
33. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant.* 2009;9 (Suppl 3):S1-155.