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Monoclonal Gammopathy of Undetermined Significance after Kidney Transplantation: single-center experience

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-Leonardo Potenza, Mario Luppi and Gianni Cappelli interpreted the data and reviewed the work critically.

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Abbreviations

CKD, chronic kidney disease

CMV: cytomegalovirus

EBV, Epstein - Barr virus

HBV, hepatitis B virus

HCV, hepatitis C virus

MBL, monoclonal B cell lymphocytosis

MGUS, monoclonal gammopathy of undetermined significance

MM, multiple myeloma

KT, kidney transplantation

PTLD, posttransplant lymphoproliferative disorders

SPEP, serum protein electrophoresis

Abstract

Background*:** Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic premalignant plasma cell disorder. Prevalence and clinical outcomes of MGUS in kidney transplant (KT) recipients have been previously reported in few studies with conflicting results. ***Methods: We conducted a retrospective study in a population of 548 KT recipients transplanted between 1998 and 2015. ***Results:*** Thirty-nine subjects (8.1%) developed MGUS after KT. At diagnosis of MGUS, the average age was 52±9.2 years and 23% of patients were younger than 50 years. Occurrence of MGUS was not influenced by age and sex. After a mean follow-up of 7.8 years, only 1 patient (2.5%) progressed to multiple myeloma. We found no differences in the incidence of solid and hematological malignancies, serious infections, graft failure and mortality between KT patients with MGUS and a matched cohort of KT recipients without MGUS. The MGUS group had a significantly higher prevalence of Monoclonal B cell Lymphocytosis (MBL), premalignant condition poorly described in KT recipients. Prior history of glomerulonephritis or interstitial nephritis, as cause of renal failure, represented the only predictive factor for MGUS development. ***Conclusions*:** MGUS is a premalignant disorder frequently encountered in KT recipients; we found no differences in clinical outcomes between MGUS patients and KT controls.

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic premalignant plasma cell disorder associated with an increased relative risk for later development of multiple myeloma (MM) and other lymphoproliferative diseases [1]. MGUS is defined by a monoclonal immunoglobulin concentration in serum of 3 g per deciliter or less, a proportion of plasma cells in the bone marrow of 10 percent or less and the absence of lytic bone lesion, anemia, hypercalcemia, and renal insufficiency related to the proliferation of monoclonal plasma cells[2]. A recent consensus conference reported a prevalence of MGUS of about 3-4% in the general population above 50 years of age [3]. The condition is reported to be infrequent before 50 years of age, has a higher incidence in males and African-Americans and carries a risk of transformation to multiple myeloma (MM) of about 1% per year [2,4–6].

Although MGUS has been largely evaluated in general population-based studies, its prevalence and course in organ transplant recipients remains largely unknown. Prevalence of MGUS after kidney transplantation (KT) has been assessed in few studies, with conflicting results. Passweg et al,[7] showed a 5-years cumulative incidence of MGUS after KT of 10.7%, much higher than expected for a group of similar age from the general population; more recently Cuellar-Garcia et al,[8] and Bancu et al,[9] reported respectively a 2.9% and a 1.57% prevalence of MGUS after KT. Development of MGUS have been associated with more intense immunosuppression[7]; no transformations to MM were reported[7–9] and very few posttransplant lymphoproliferative disorders (PTLDs) have been described in transplanted patients with MGUS[8,10]. A substantial proportion of post-KT MGUS has been reported to spontaneously disappear during follow-up[7–9]. Of note, the presence of MGUS conferred a higher risk for serious

infections, incidence of chronic kidney disease (CKD) and mortality in a population of liver transplant recipients[11].

Based on this background, the aim of our study was to assess the prevalence of MGUS in a population of KT recipients, evaluating its association with clinically significant outcomes.

Materials and Methods

After the approval of Institutional Review Board, we retrospectively reviewed medical charts of 548 patients who received a KT between January 1998 and December 2015 at Policlinico of Modena, Italy. All patients underwent regular follow-up at our center.

Diagnosis of MGUS was suspected based on a positive serum protein electrophoresis (SPEP), and subsequently confirmed and typed by serum immunofixation; urine protein electrophoresis and immunofixation were used on single voided urine specimen to detect and Bence-Jones protein. Starting from 2011, in accordance with our local protocol, serum free light-chain assay was performed in patients with newly diagnosed MGUS, while peripheral blood flow cytometry was carried out in all patients with MGUS irrespective of time of diagnosis. MGUS was defined as transient if the monoclonal protein spontaneously disappeared during follow-up; otherwise, it was referred as stable.

The performance of SPEP was not generally requested for asymptomatic patients to get on transplant waiting list at our center; nevertheless, it was always included in preoperative blood tests aiming at early identification of MGUS, well described premalignant condition.

During follow-up, local protocol included the performance of SPEP twice a year, regardless of the diagnosis of MGUS. Patients who had annual follow-up (ie, patients residing far from our center) were tested with SPEP at least yearly. Technically, agarose gel electrophoresis was used until 2004 after which it was replaced by capillary gel electrophoresis.

At time of diagnosis of monoclonal gammopathy, each subject was refereed to our collaborative hematologist for diagnosis assessment, risk stratification and management of the lymphoproliferative condition. Bone marrow aspirate and biopsy were performed in patients with a monoclonal protein value ≥ 1.5 g/dl and in patients who had an unexplained anemia, renal insufficiency, hypercalcemia, or bone lesion or a suspicion of light-chain amyloidosis. Starting from 2011, bone marrow aspirate and biopsy were performed also in patients with non-IgG MGUS, or with abnormal free light chain ratio, as recommended by international guidelines[12].

After exclusion of patients with a minimum follow-up shorter than 6 months after KT, patients with HIV infection, patients who received a combined kidney-liver transplant, patients who had MGUS before KT and patients with a transient monoclonal immunoglobulin, we analyzed demographics and characteristics of monoclonal protein in KT recipients with stable MGUS after KT. Subsequently, we compared this group of patients with a control population of KT recipients matched for sex, age and transplant date in a matched case-control analysis. We analyzed the following outcomes: death with functioning graft, graft failure (defined as the need of maintenance dialysis), incidence of solid and hematological malignant neoplasms, incidence of Monoclonal B cell lymphocytosis (MBL), incidence of biopsy-proven rejection, development of CKD stage IV (defined as CKD-EPI estimated GFR < 30 ml/min after at least 6 months from

KT and for more than 6 consecutive months), incidence of serious infectious events (defined as hospitalization plus laboratory evidence of invasive bacterial, viral or fungal infection requiring intravenous specific antimicrobial or supportive treatment).

MBL was detected by 6-color flow cytometry using a sequential gating strategy. The scan was not equipped to detect minimal residual disease. The diagnosis of MBL relayed on the identification of a light chain restricted B cell lymphocytosis in which the absolute lymphocyte number was less than 5×10^9/L in absence of other lymphoproliferative, infectious or autoimmune disorders.

Hepatitis C virus (HCV), Hepatitis B virus (HBV), Cytomegalovirus (CMV), Epstein-Barr Virus (EBV) plasma replication and BK and JC virus plasma and urine replication were assessed by Real-Time Reverse Transcription-PCR assay. We considered the test as positive at any level of viral loads above detection limit. Furthermore, we investigated potential predictors of the development of MGUS.

Statistical analysis was performed using the GraphPad Prism 6 and the SPSS 21 software. Prevalence data were expressed as percentages; continuous data were expressed as mean ± standard deviation, unless otherwise stated. In the matched case-control analysis continuous data were compared with t student test, while categorical data were compared either with Chi-squared test or Fisher's exact test as appropriate; differences in event-free survival were estimated using the Kaplan-Meier method with log-rank test. Univariate logistic regression was used to identify potential predictive factors for the development of MGUS.

Results

Prevalence and laboratory characteristics

Based on the exclusion criteria mentioned above, 479 of the 548 transplanted patients were considered suitable for evaluation. MGUS was detected in 55 subjects. Twelve patients had a transient monoclonal protein and were excluded from further analysis. Among 43 patients with stable MGUS, 4 presented the condition before KT and were not considered in our study. We focused on 39 patients (8.1% of analyzed population) who developed a stable MGUS after KT. Their clinical and demographic characteristics are reported in table 1. The mean age at diagnosis was 57 ± 9.7 years; of note, 23% of patients were younger than 50 years (see table 1). Interestingly, we encountered a similar rate of MGUS development between age classes (see table S1, SDC, http://links.lww.com/TP/B468). Although a male predominance was apparent in the MGUS population, we found no sex difference in the prevalence of MGUS after KT; indeed, 27 cases were men (8,2% of transplanted male population) and 12 were women (8,2% of transplanted female population). The median time from KT to the appearance of MGUS was 5.3 ± 4.6 years during a median follow-up of 5.9 ± 5.2 years. Characteristics of the monoclonal proteins are listed in table 2. Monoclonal protein was most often of the IgG subtype (54%), as expected; of note, the monoclonal immunoglobulin was bi-clonal in 26% of the 39 patients, and in 1 patient (2%) was tri-clonal. One case of light chain MGUS was detected by abnormal free light-chain ratio following a doubt identification of a monoclonal immunoglobulin at SPEP test. Fifteen patients developed Bence-Jones proteinuria, with a higher prevalence for the the λ isotype (47%). The mean serum monoclonal protein level was 0.58 gr/dl, with values ranging from immeasurable to 2.1 gr/dl; serum levels of monoclonal proteins remained substantially stable over time (data not shown).

Bone marrow aspirate and biopsy were performed in 6 patients with MGUS. In 5 out of 6 cases, clonal bone marrow plasma cells were less than 10%, whereas in 1 case multiple myeloma was diagnosed.

In patients with MGUS flow cytometry analysis of bone marrow cells showed the absence of any significant alteration. During follow-up, no patients had bone marrow biopsy or laboratory characteristics suggestive for smoldering myeloma; 1 patient developed a PTLD (specifically, low-grade non-Hodgkin lymphoma) after the diagnosis of MGUS.

Serum-free light chain dosing was available only in a minority of patients and therefore was not included in the analysis.

Clinical outcomes: matched case-control analysis

We compared the 39 KT patients with stable MGUS with 79 matched KT recipients who did not develop MGUS. As expressed in table 3a, there were no significant differences in age, gender and mean duration of follow-up between the 2 groups; types of immunosuppressive regimens and number of human leukocyte antigens (HLA) mismatches were also similar, as was the prevalence of main viral infections.

As reported in table 3b, the incidences of hematological and solid neoplasms (including skin malignancies) were similar in both groups. On the other hand, the MUGS group presented a significantly higher prevalence of MBL, an asymptomatic premalignant condition characterized by the expansion of a clonal B cell population [13].

Of note, patients with MGUS were tested significantly more frequently with peripheral blood flow-cytometry compared to controls (77% vs 19%, p= <0.0001).

The rate of serious infectious events was slightly higher in the MGUS group, although the difference was not statistically significant. There was no difference in the overall incidence of biopsy-proven rejection between the 2 groups. Furthermore, it is worth to note that the ten cases of rejection (91%) preceded the diagnosis of MGUS by a mean age of 5 years. KT patients with MGUS had a slightly higher risk of developing CKD stage IV, but the difference with the control group was not significant. Graft and overall survival after KT were not significantly different among patients with MGUS and controls, as exemplified by the Kaplan-Meyer curves in figure 1 and figure 2. In the univariate logistic regression, reported in table 4, the only factor potentially associated with the development of MGUS after KT was a positive history for inflammatory kidney disease (glomerulonephritis or acute interstitial nephritis) before KT.

Discussion

Prevalence of MGUS after KT is unclear and mainly based on small single-center descriptions. Exposure to immunosuppressive treatment could theoretically contribute to a higher prevalence of MGUS in KT recipients, as already noted[7]; notwithstanding, the few studies conducted in recent years reported opposite findings[8,9]. Moreover, risk factors for MGUS development have not been clearly identified and the prognosis of this condition after solid organ transplantation remains elusive. Although some authors suggest a benign course for this condition[14], there are few reports about its potential association with hematologic

malignancies[8,10,15], and a recent study performed in liver transplant recipients described a higher incidence of medical complications in patients with MGUS[11].

As previously noted, serum monoclonal proteins can frequently be transient after transplantation[7,8], much more than what reported for the general population. A consistent number of our patients had a MGUS that spontaneously disappeared during the follow-up; although it was not possible to trace all changes made to pharmacologic treatments, modulations in the immunosuppressive therapy dose may account for this phenomenon. Assuming that a transient condition should not bear substantial clinical implications, we focused our attention on the group of patients diagnosed with stable MGUS after KT.

The overall prevalence of patients with stable MGUS after KT in the present study was 8.1%, much higher than what reported in the general population. The age-specific analysis demonstrated a nonsignificant difference in MGUS prevalence between age classes in our group (see table S1, SDC, http://links.lww.com/TP/B468), contrasting again with reports on the common clinical course of the condition in nontransplanted subjects. It is relevant to note that 9 patients (23%) were younger than 50 years, differing strikingly from general population, where the condition is fairly uncommon before 50 years of age[2,4]. Our findings are in line with a previous report from Braun et al,[16] describing a high prevalence of monoclonal gammopathy in relatively young (mean age 53.4 years) KT recipients with a functioning graft for more than 30 years. The distribution of MGUS after KT was not gender specific, while population-based studies reported the condition to be more prevalent in males[2,4]. Thus, KT seems to act as a predisposing factor for the development of MGUS irrespective of age and gender. We speculate

that the reduced immunologic surveillance due to the immunosuppressive treatment may possibly favor the proliferation of a plasma cell clone in susceptible KT recipients.

The median time from KT to the appearance of the MGUS was 5.2 years, in contrast with a previous study[7], where a shorter time lapse was reported; this difference is likely related to the more aggressive induction treatments used in the early transplantation era there analyzed.

Distribution of the immunoglobulin isotypes in our group was similar to what reported for the general population, with a definite prevalence for the IgG class (see table 2); nevertheless, we unexpectedly encountered a very high incidence of , substantially differing from data available in normal subjects, where they account for 3% of all monoclonal proteins[2].

Although few studies identified EBV[17,18] and CMV[18] infections as potential risk factors for the development of MGUS in transplanted patients, we are not able to confirm these associations. In our study, rate of infections for EBV, CMV did not differ significantly between patients with MGUS after KT and matched KT recipients, as expressed in table 3a. In addition, we report no differences in the rate of infection of BK and JC polyomavirus between MGUS patients and controls.

We encountered no differences between the group of patients with stable MGUS and a matched cohort of KT recipients with respect to strong outcomes, such as mortality and graft failure (as depicted in Figure 1 and Figure 2). Rate of development of “de novo” malignancies, both hematological and solid cancers, were similar between the 2 groups (as reported in table

3b), in accordance with data previously reported in liver transplant recipients[11]. Of note, only 1 patient developed fatal MM after 1.5 years from transplant and 1 month from MGUS diagnosis.

On the other hand, MUGS group presented a higher rate of MBL, premalignant condition which can predispose to the development of chronic lymphocytic leukemia and other lymphoproliferative malignancies[13,19,20]; nevertheless, the strength of this association is dampened by the fact that MGUS patients were tested more often with peripheral blood flow cytometry than controls. Based on our experience, we believe that these findings should prompt regular hematological follow-up in in KT recipients with MGUS. Monitoring of the monoclonal protein blood levels and performance of flow cytometry for early detection of B lymphocytic clones should be advised; clinicians should maintain a high degree of suspicion for malignancy during follow-up of these patients.

Similar to what reported by Galioto et al,[11] who described an increased rate of infections in liver transplant recipients with MGUS, our patients in the MGUS group had a slightly higher, although not significant, incidence of serious infectious events (see table 3b). In a large epidemiologic study performed in Sweden, normal subjects with MGUS were reported to be at increased risk for bacterial infections irrespective of serum monoclonal protein level, supporting the hypothesis of an underlying state of immunodeficiency in this condition[21]. This predisposition, combined with the detrimental effects of immunosuppressive therapy in transplanted patients may further worsen their immunologic competence.

Considering the incidence of biopsy-proven rejection, groups did not differ significantly; it was interesting to note that in the MGUS group 91% of rejection episodes preceded the diagnosis of MGUS, suggesting that the incremented immunosuppression imposed by the biopsy findings might have played a role in the development of the monoclonal gammopathy.

The only predictive factor for the development of MGUS after KT in the univariate analysis was a pretransplant history of inflammatory kidney diseases (glomerulonephritis or acute interstitial nephritis); we speculate that previous exposure to immunosuppressive agents commonly used to treat these conditions, although difficult to quantify, may contribute to the development of a monoclonal plasma cell clone after KT. Moreover, autoimmune connective tissue disorders, frequently cause of immune-related renal diseases, and inflammatory disorder including glomerulonephritis, have been associated with an increased risk of MGUS development in population based-studies[22,23]. On the other hand, more plausible risk factors such as previous viral infections and different immunosuppressive protocols, already identified in previous studies[7,17,18], were not associated with development of MGUS after KT in our patients, as reported in table 4.

Our study has some limitations that should be acknowledged: shortness of follow-up, relatively small number of cases and retrospective design of our analysis must be taken into account before considering these results as conclusive.

In conclusion, we report a high incidence of stable MGUS after KT (8.1%). Differently from general population, the occurrence of MGUS was not influenced by age and gender, with a

considerable number of cases developing in young subjects. The burden of immunosuppressive treatment posttransplantation and the prior history of inflammatory kidney disease may cause immune dysregulation and favor the development of a plasma cell clone. The presence of MGUS did not impact on graft survival, overall survival and incidence of malignancies; there was a slight, although nonsignificant, increase in the cumulative incidence of serious infections. Although MGUS did not show a very aggressive course in terms of frank progression to MM, we found a significant increase in the incidence of MBL, premalignant condition which warrants a strict hematological follow-up in KT patients. Further studies are needed to elucidate the complex epidemiologic characteristics of MGUS developed after KT and to confirm its association with MBL.

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Ethics approval and consent to participate

The study was approved by the Ethics Committee of Policlinico of Modena (Prot. n° 1476/ C.E.) and written informed consent was obtained from all participants prior to any study procedures.

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Figure 1: Kaplan-Meyer plot for overall survival in KT recipients with stable MGUS and matched KT controls.

Figure 2: Kaplan-Meyer plot for graft survival in KT recipients with stable MGUS and matched KT controls.

Figure 1.

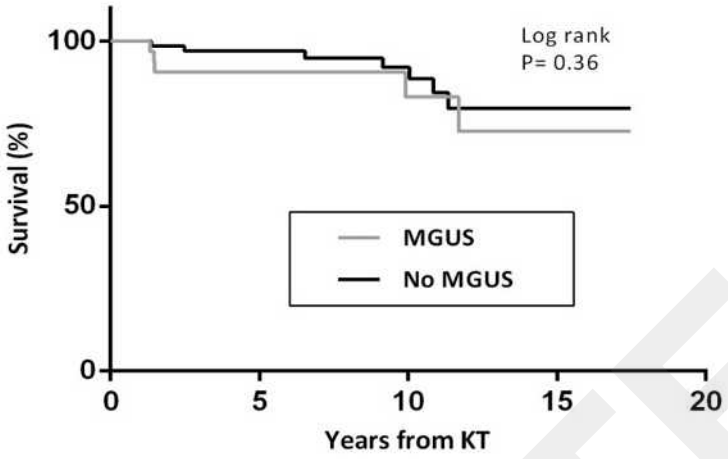

Figure 2.

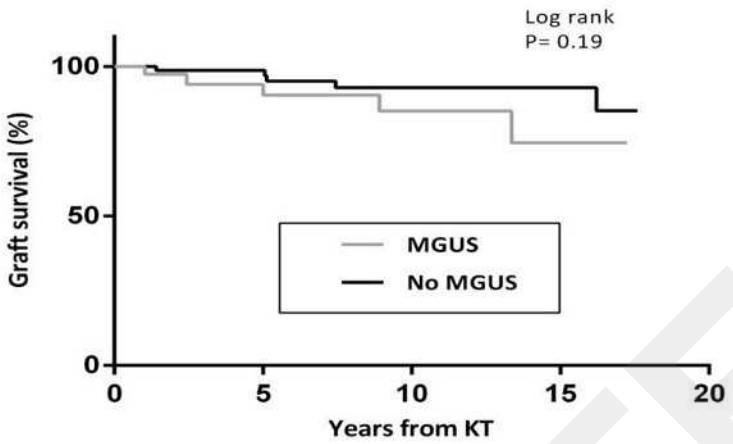

Table 1: Demographic and clinical characteristics of 39 subjects with stable MGUS after KT.

Age	
< 50 years	23%
> 50 years	77%
Mean (yr)	52 ± 9.2
Range (yr)	32-75
Sex	
Male	69%
Ethnicity n. (%)	
Caucasian	38 (97%)
African	1 (3%)
Viral infection	
HBV	0 (0%)
HCV	2 (5%)
Kidney transplantation n.(%)	
Living-donor transplantation	2 (6%)
Single-kidney transplantation	34 (87%)
Double-kidney transplantation	3 (8%)
Laboratory tests	
Serum creatinine (mg/dl)	2.14 ± 1
Estimated GFR (ml/min)	39 ± 13
Leukocytes count (/ul)	6850 ± 2000
Hemoglobin count (mg/dl)	12.1 ± 1.6
Platelet count (/ul)	175 000 ± 60 000
Calcium level (mg/dl)	9.5 ± 0.7
Albumin level (g/dl)	3.9 ± 0.5
Induction therapy n. (%)	
None	9 (23%)
Basiliximab	28 (72%)
Antithymocyte globulin	2 (5%)
Immunosuppressive therapy at the diagnosis of MGUS	
Calcineurin inhibitor	83%
mTOR inhibitor	36%
Glucocorticoid	79%
Antimetabolite	33%

HCV: Hepatitis C Virus, HBV: Hepatitis B Virus
Plus-minus values are means ± SD.

† The glomerular filtration rate (GFR) was estimated with the use of Chronic Kidney Disease Epidemiology Collaboration equation.

Table 2: MGUS characteristics of the 39 subjects with stable MGUS after KT.

Serum immunoglobulin isotype (%)	
IgG	54%
IgM	11%
IgA	5%
biclonal	26%
triclonal	2%
λ (light chain MGUS)	2%
Positive Bence-Jones protein	15 (38%)
Urine immunoglobulin isotype (%)	
light chain λ	47%
light chain k	33%
biclonal	13%
light chain plus heavy chain	7%
Monoclonal protein(g/dl)	
Mean	0.58±9
Range	<0.5-2,1
Interval between diagnosis of MGUS and transplantation (years)	
Mean	5.3±4.6
Bone marrow biopsy n.(%)	6 (15%)
Progression to smoldering multiple myeloma n.(%)	0 (0%)
Progression to multiple myeloma n.(%)	1 (1%)

Table 3: a) Comparison of demographic and clinical characteristics between MGUS subjects and matched KT recipients. **b)** Comparison of clinical outcomes between MGUS subjects and matched KT recipients.

a	MGUS subjects (n. 39)	KT recipients (n.79)	p
Age at KT (years)	52	49	NS
Mean follow-up KT (years)	7.8	8.2	NS
Male n. (%)	29 (70%)	50 (72%)	NS
Induction agent: none/basiliximab/thymoglobulin (%)	15/80/5	11/78/11	NS
Basal agent: CsA/FK/mTOR-i (%)	67/33/0	68/29/3	NS
mTOR-i (%)†	23%	19%	NS
HLA mismatch‡	3 (1.1)	2.9 (1.1)	NS
Viral replication (+/ subjects tested) (%)			
HCV	2/39 (5%)	2/79 (3%)	NS
EBV	18/29 (62%)	21/33 (64%)	NS
CMV	18/39 (46%)	30/79 (38%)	NS
Urinary BK Polyomavirus	13/33 (39%)	22/58 (38%)	NS
Serum BK Polyomavirus	3/13 (23%)	3/22 (14%)	NS
Serum JC Polyomavirus	4/17 (24%)	10/29 (34%)	NS
Biopsy-proven rejection: n. (%)	11 (28%)	14 (36%)	NS

b	MGUS subjects (n. 39)	KT recipients (n.79)	p
Hematological malignancy	2 (5%)	1 (1%)	NS
Nonhematological malignancy	7 (18%)	14 (18%)	NS
• Skin malignancy	2	7	NS
• Nonskin malignancy	5	7	NS
Monoclonal B cell lymphocytosis	3 (8%)	0 (%)	**0.034**
Mortality: n. (%)	5 (13%)	7 (9%)	NS
Due to malignancy: n. (%)	3	3	NS
Due to infections: n. (%)	1	1	NS
Due to cardiovascular causes	1	2	NS
Due to other causes	0	1	NS
GFR* < 30ml/min n. (%)	9 (23%)	11 (14%)	NS
GFR* < 15ml/min n. (%)	2 (5%)	3 (4%)	NS
Dialysis	5 (13%)	5 (6%)	NS
Serious infectious events	17 (44%)	23 (29%)	NS

CsA: Cyclosporine; FK: Tacrolimus; mTOR-i: Mammalian Target of Rapamycin inhibitors; KT: Kidney transplant; HCV: Herpes C Virus; EBV: Epstein-Barr Virus; CMV: Cytomegalovirus

* The glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

† Use of mTOR-i as first agent or as second agent to minimize calcineurin inhibitor.

‡ Human leukocyte antigen mismatch recipient/donator.

Table 4. Analysis of potential predictive factors for MGUS

	OR	CI	P
Male/female	1.3	0.57-2.96	0.524
Previous infiammatory renal disease	2.73	1.18-6.35	**0.019**
Time spent in dialysis	1.10	0.97-1.24	0.114
Graft-age	0.99	0.92-1.06	0.822
CMV infection	1.4	0.64-3.04	0.396
EBV infection	0.93	0.33-2.62	0.899
HLA mismatch	1.06	0.75-1.5	0.72
Anti-CD52 vs. thymoglobulin as induction	0.48	0.21-1.09	0.82
CsA vs.FK as basal IM agent	0.852	0.37-1.94	0.7
mTOR as IM agent	1.28	0.50-3.25	0.64
Two vs. 3 agent for IM	1.33	0.44-4.06	0.606

IM: immunosuppression; KT: kidney transplant; HLA: human leukocyte agent; CsA: cyclosporine, FK: tacrolimus.

Table S1: Age and sex specific rate among MGUS subjects over KT population. Rates of MGUS in age classes were compared using Chi-squared test and no significant differences were encountered (p=0.19).

Age	Men (MGUS/KT recipient)	Women (MGUS/KT recipient)	Total (MGUS/KT recipient)
<29 yr	0/10 (0%)	0/4 (0%)	0/14 (0%)
30-39 yr	2/40 (5%)	0/14 (0%)	2/44 (5%)
40-49 yr	5/58 (8%)	2/34 (6%)	7/92 (8%)
50-59 yr	9/77 (12%)	5/40 (12%)	14/117 (12%)
60-69 yr	9/92 (10%)	5/40 (15%)	14/132 (11%)
>70 yr	2/51(4%)	0/15 (0%)	2/66 (3%)
	27/328 (8.2%)	12/147 (8.2%)	39/475* (8.1%)

* Four of 479 subjects of were censored from overall KT population because they had diagnosis of MGUS pretransplant.