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Original Article

ORIGINAL ARTICLE

Monoclonal gammopathy of undetermined significance coexisting in patients undergoing kidney transplantation does not adversely influence post-graft clinical outcome

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ABSTRACT

Background. Management of patients with oncohaematological disorders such as monoclonal gammopathy of undetermined significance (MGUS) is a frequent problem in pre-transplant work-up. Insights on disease progression and long-term functional outcomes are still lacking in this setting.

Methods. This was a retrospective analysis on all patients with MGUS who underwent kidney transplant (KT) at our centre between 1 January 2000 and 31 December 2017 (cases, $n = 65$). Patients were matched with a control group (KTs with similar characteristics but without history of haematological disease, controls, $n = 1079$). Primary endpoints were graft and patient survival; secondary endpoints were causes of graft failure, patient death, occurrence of allograft rejection, post-transplant neoplasia (not correlated to previous disorder) and/or infectious episodes.

Results. The MGUS and control groups had a similar mean age [60 (29–79) versus 55.2 (19.3–79.5) years, respectively] and percentage of males (69.2% versus 64.6%, respectively). Median follow-up time since KT was 3.5 years (0–14) in cases and 8.3 years (0–14.9) in controls. All MGUS patients underwent KT following extensive multidiscliplinary investigations. No differences were found between cases and controls regarding patient and graft survival or post-transplant complications except for lower incidence of infections (58.7% versus 69.8%, $P = 0.019$) and increased use of mTOR inhbitors (30.3% versus 14.7%, $P = 0.001$) in MGUS. MGUS isotype did not influence graft and patient survival. The absence of difference in patients

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and graft survival was also confirmed in an adjunctive analysis where MGUS were compared with controls (ratio 1:2) matched for recipient age, gender, number of transplantations and transplant period.

Conclusion. Patients with MGUS may undergo KT without significantly increased risks of complications, provided that appropriate diagnostic procedures are carefully followed. Multidiscipline-based studies are crucial for establishing well designed pre- and post-transplant protocols for the best management of patients with coexisting MGUS and end-stage renal disease.

Keywords: graft function, graft survival, immunosuppression, kidney transplantation, mTOR, multiple myeloma, survival analysis

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem with a continuously increasing prevalence of end-stage renal disease (ESRD) despite a stabilized incidence [1]. Kidney transplant (KT) currently remains the best renal replacement therapy. Although the risk of rejection has progressively decreased over time due to improvements of immunosuppressive therapies, the prolonged exposure to such therapies has produced an increase in infectious and neoplastic risks, with incidence of cancer three to five times higher than in general population [2]. Patients therefore need to be carefully evaluated before KT.

Due to progressive lengthening of the average life expectancy and improvements in therapies and survival rate of many neoplastic diseases, oncohaematological disorders are now one of the most frequent conditions to deal with in pre-transplant work-up. In particular, the co-existence of monoclonal gammopathy of undetermined significance (MGUS) is a rather frequent finding. Despite the increasing incidence of this condition, information regarding the long-term outcome of MGUS patients following KT is still scarce. So far, most studies on MGUS and KT have dealt with case reports or case series with limited sample size, in the absence of comparative analysis with adequate control groups [3–6]. Indeed, exhaustive specific indications are lacking in international guidelines about pre-transplant and post-transplant management of patients with MGUS unrelated to the underlying ESRD [7–12].

In this study, a retrospective analysis has been performed in patients undergoing KT with a previous diagnosis of MGUS. The study aimed to evaluate whether the presence of MGUS might affect overall and organ survival. The behaviour of the haematological disorder and the incidence of post-transplant complications following KT were investigated as well. Moreover, it has been possible to compare the MGUS series with a control KT population displaying similar characteristics without a history of oncohaematological diseases.

MATERIALS AND METHODS

Study design

The study has included 2034 KTs, from either deceased or living donors, performed at Turin University Renal Transplant Centre 'A. Vercellone' from January 2000 to December 2017. Patients with a pre-transplant MGUS diagnosis (cases) were identified and analysed separately. MGUS diagnosis was based on laboratory parameters, namely: serum electrophoresis, serum and urinary immunofixation, free light kappa and lambda chain determination, and, if available, bone marrow (BM) evaluation. As policy of our Centre, patients with MGUS that is the cause of ESRD are not eligible for KT. Indeed, all patients included in this study had ESRD unrelated to the coexistent MGUS.

Data were collected from patient's individual charts at the time of KT and at 1-, 2-, 5- and 10-year follow-up, and at the last follow-up visit in our post-transplant outpatient unit.

For each patient, we retrospectively reviewed sex, age, underlying nephropathy, type of dialysis and its duration before KT, previous transplant or immunosuppressive therapies, type of transplant (deceased or living donor), immunosuppressive therapy and post-transplant graft function [serum creatinine (sCr) and 24 h proteinuria (Pto)]. Data regarding the haematological disorder were collected as well, including monoclonal gammopathy isotype, time of onset before KT, follow-up and occurrence of post-transplant haematological progression. Follow-up ended in May 2018.

A matched cohort analysis was performed considering a selected population of patients with similar baseline characteristics at KT (age at transplant, sex, type of dialysis, graft function at discharge) without pre-transplant oncohaematological disorders. A comparative analysis among MGUS isotypes was performed as well.

Primary outcomes were graft and patient survival. Secondary endpoints were causes of graft failure and patient death as well as the occurrence of allograft rejection, secondary neoplastic diseases and infectious complications.

Considering the high number of control patients, an adjunctive analysis adopting a selected cohort of controls (ratio of MGUS:controls, 1:2) matched for recipient age, gender, number of transplantation and transplant period was also conducted in order to reduce the bias due to potentially confounding variables.

This study was performed in adherence with the last version of the Helsinki Declaration and with the Principles of the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Statistical methods

Discrete data were described as percentages and analysed with Pearson Chi-squared test or for small samples, Fisher's exact test. Continuous variables were described as median (min–max). Mann–Whitney and Kruskal–Wallis test were used when appropriate. Cumulative graft and patient survival were analysed by Kaplan–Meier (KM) curves and log-rank test. According to the KM model only independent events were included (i.e. KTs >1 were excluded).

An adjunctive analysis was carried out adopting a manually selected cohort of controls. The matching ratio was 1:2 and the considered variables included recipient age and gender, number of transplantation and transplant period. Statistical analyses were performed using SPSS software, version 22 (SPSS, Inc., Chicago IL, USA, version 25.00). Significance level for all tests was set at $P < 0.05$.

RESULTS

Population characteristics at baseline (cases and controls)

Between 1 January 2000 and 31 December 2017, 2034 KTs were performed in 1965 patients at our centre; MGUS was present at the time of KT in 65 patients (3.2%); it was not the cause of ESRD in any case. Heavy and light chain isotypes were as it follows: 28/65 (43.1%) immunoglobulin G (IgG) kappa, 15/65 (23.1%) IgG lambda, 5/65 (7.7%) IgA kappa, 1/65 (1.5%) IgA lambda, 2/65 (3.1%) IgM kappa and 2/65 (3.1%) IgM lambda; 1 patient had biclonal gammopathy (IgG kappa and IgM lambda); in 13 cases pre-transplant MGUS isotype was unknown. Urinary immunofixation was negative in 46.2%; only 12 patients had an altered kappa/lambda ratio; IgG, IgA and IgM levels were normal in most cases (55.4%, 64.6% and 55.4%, respectively). A pre-transplant BM biopsy was performed in 26 patients (38.2%). All patients had regular haematological evaluations and all MGUS patients were placed in the KT list following a thorough multidisciplinary re-assessment. Median time between MGUS diagnosis and KT was 60 (1–300) months; all patients showed stable monoclonal peak during the follow-up period before KT.

The control group includes 1079 KTs performed at our Centre between 2003 and 2013. Patient characteristics and immunosuppressive regimens at KT are summarized in Table 1: there were no differences in sex, age at KT, main underlying nephropathies and prevalence of patients on haemodialysis (HD) between the two groups. There was a significantly higher prevalence of previous KT in cases (23%) compared with controls (13.3%) ($P < 0.05$).

NS: not significant

Immunosuppressive therapy was tailored on donor and recipient characteristics: basiliximab was used as induction in 89.5% cases and 94.3% controls in association with a calcineurin inhibitor (CNI) -based regimen (97% of cases and 91.5% of controls). There was a higher use of mTOR inhibitors in cases (30.3%) than in controls (14.7%) ($P = 0.001$). Median sCr and Pto at discharge were similar between groups: 1.9 mg/dL (0.87–7.5) and 0.3 g/24 h (0.1–3) in cases, and 1.88 mg/dL (0.5–8.1) and 0.36 g/24 h (0–12) in controls, respectively.

Graft and patient survival, post-transplant complications (cases versus controls)

Median follow-up time was 3.5 years (0–14) in cases and 8.3 years (0–14.9) in controls.

Functional data during follow-up were similar between groups. No differences were found in rates of allograft rejection (10.8% in cases versus 15.6% in controls, $P = 0.59$) and post-transplant neoplasia (16.7% in cases and 21.7% in controls, $P = 0.33$). Incidence of infectious complications was significantly higher in control group (69.8 versus 56.1, $P = 0.019$) (Table 2).

No differences were found between the two groups in graft and patient survival (Figure 1 and Table 2): overall, 8/65 cases and 228/1079 controls had graft loss ($P = 0.25$); 7/65 cases and 204/1079 controls died ($P = 0.17$). Among MGUS cases, three patients died due to severe infectious complication, one died from cardiovascular accident, one from respiratory distress and one from hepatic failure; cause of death was unknown for the last fatal event. Among controls, the main causes of death were infectious diseases (14.2%) and cardiovascular accident (12.3%).

Graft and patient survival were also similar in the adjunctive analysis with manually selected control cohort (Supplementary data, Figures S1 and S2).

Table 3 summarizes haematological parameters at diagnosis and during follow-up in the 65 patients with MGUS at KT. No patient showed MGUS progression and in 19 patients (29.2%) the monoclonal component disappeared after KT. In many patients, no specific evaluation of MGUS was performed during post-transplant follow-up at definite time points.

MGUS isotype did not influence graft and patient survival (Figure 2a and b).

DISCUSSION

In this matched cohort study, we investigate the role of MGUS on patient and graft survival. Our findings demonstrate the absence of a direct effect of MGUS on both patients and kidney survival, suggesting that subjects with MGUS may undergo KT without significantly increased risks of complications.

MGUS is defined by the presence of a serum monoclonal protein (IgG, IgM, IgA, IgD, with kappa or lambda light chain) in an abnormal but small concentration (≤3 g/dL), along with <10% plasma cells infiltration in BM (when determined), a small amount or absence of urinary light chains, and no clinical organ damage. In particular, MGUS does not show the typical multiple myeloma (MM) signs, included under the term CRAB, namely hypercalcaemia, renal failure, anaemia, lytic bone lesions. A small percentage of MGUS patients (3%) have indeed bi-clonal rather than monoclonal gammopathy. MGUS is typically detected as an incidental finding when patients undergo a protein electrophoresis as part of a routine evaluation or during diagnostic procedures for a wide variety of clinical symptoms and disorders. MGUS frequency is quite variable, depending on the strength of the employed screening test and in general MGUS may occur in >3% of the general Caucasian population over the age of 50 years, with an incidence slowly increasing with age [3, 13]. It is usually considered as a benign condition, but it can also progress to MM, amyloidosis, macroglobulinaemia, light chain deposition disease or lymphoplasmocytic cell proliferative disease, with a progression rate of 1–1.5%/year in the absence of immunosuppression. Isotype and serum M-component concentration are considered as the most important risk factors for progression to a malignant disease [3, 4, 14, 15]. More recently, the degree of immunoparesis, i.e. the reduction of uninvolved immunoglobulins below lower level of normal, has been reported as a relevant prognostic factor [16].

MGUS represents nowadays one of the most frequent onco-haematological problem that must be dealt with while evaluating patients for KT. The main issue raised in case of MGUS detection is the risk of progression towards patent lymphoproliferative disorder as a consequence of the immunosuppressive post-KT therapy. Furthermore, the influence of the monoclonal gammopathy on KT outcome, in terms of both graft and patient survival and risk of post-transplant complication, has not been fully addressed.

In 2012, the International Kidney and Monoclonal Gammopathy Research Group (IKMG) introduced the new expression ‘monoclonal gammopathy of renal significance’ (MGRS) to describe cases that would otherwise meet the criteria for MGUS, but demonstrate renal insufficiency directly related to the presence of monoclonal immunoglobulin deposits in the kidney proved by immunofluorescence [17]. The IKMG met again in April 2017 and redefined MGRS as any B-cell or plasma cell clonal lymphoproliferation that does not cause tumour complications or meet any current haematological criteria for specific therapy and is associated with one or more kidney lesions. These latter can be induced either by monoclonal Ig

Table 1. Patients characteristics and immunosuppressive regimens at KT

Clinical variables	MGUS ($n = 65$)	Controls ($n = 1079$)
Men/women, *n* (%)	45 (69.2)/20 (30.8)	697 (64.6)/382 (35.4)
Age at KT, median, years	60 (29–79)	55.2 (19.3–79.5)
Underlying nephropathy		
Diabetic nephropathy, *n* (%)	4 (6.2)	47 (4.4)
Nephroangiosclerosis, *n* (%)	5 (7.7)	122 (11.3)
Glomerulonephritis, *n* (%)	18 (27.7)	355 (32.9)
Tubulo-interstitial disease, *n* (%)	5 (7.7)	114 (10.6)
APKD, *n* (%)	8 (12.3)	163 (15.1)
Not known, *n* (%)	21 (32.3)	171 (15.8)
Urological disease, *n* (%)	2 (3.1)	0
Malformative disease, *n* (%)	2 (3.1)	13 (1.2)
Other, *n* (%)	0	94 (8.7)
Type of dialysis		
HD, *n* (%)	48 (73.8)	834 (77.3)
PD, *n* (%)	8 (12.3)	245 (22.7)
HD+PD, *n* (%)	8 (12.3)	NA
Preemptive, *n* (%)	1 (1.5)	NA
Dialysis before KT, median, years	3 (0.5–22)	NA
Previous KT, *n* (%)	15 (23)	143 (13.3)
Previous immunosuppressive therapies, %	29 (44.6)	NA
Living/cadaveric donor, %	4 (6.2)/61 (93.8)	NA
Induction immunosuppressive therapy		
ATG, *n* (%)	2 (3)	5 (0.5)
Basiliximab, *n* (%)	58 (89.5)	1018 (94.3)
ATG + basiliximab, *n* (%)	4 (6)	15 (1.4)
Daclizumab, *n* (%)	1 (1.5)	0
St only, *n* (%)	0	15 (1.4)
Not known, *n* (%)	0	26 (2.4)
Immunosuppression at discharge		
CNI + MMF + St, *n* (%)	52 (80)	688 (63.8)
CNI + St, *n* (%)	6 (9.2)	228 (21.1)
CNI + mTOR inhibitor + St, *n* (%)	5 (7.7)	50 (4.6)
CNI + AZA, *n* (%)	0	0
mTOR inhibitor + MMF + St, *n* (%)	2 (3.1)	24 (2.2)
St only, *n* (%)	0	0
CNI + AZA + St, *n* (%)	0	19 (1.8)
CNI + MMF, *n* (%)	0	1 (0.1)
CNI only, *n* (%)	0	1 (0.1)
MMF + St, *n* (%)	0	13 (1.2)
mTOR inhibitor + St, *n* (%)	0	1 (0.1)
NA, *n* (%)	0	54 (5)
sCr at discharge, median, mg/dL	1.9 (0.87–7.5)	1.88 (0.5–8.1)
Pto at discharge, median, g/24 h	0.3 (0.1–3)	0.36 (0–12)

APKD, autosominal-dominant polycystic kidney disease, PD, peritoneal dialysis; NA, not available; ATG, anti-thymocyte globulin; AZA, azathioprine; MMF, mycophenolate mofetil; St, steroids.

deposition in renal tissue or by its activity as autoantibody [18, 19]. This definition includes many different renal diseases such as renal amyloidosis, fibrillar glomerulopathy, immunotactoid glomerulopathy, cryoglobulinaemic glomerulonephritis Types I and II, monoclonal immunoglobulin deposition disease, glomerulonephritis associated with monoclonal immunoglobulin (proliferative, membranoproliferative, membranous, C3 nephritis and C4 dense deposit disease), tubulopathies like light chain Fanconi syndrome, and atypical haemolytic uraemic syndrome. Besides an increased morbidity and mortality, MGRS is characterized by a high risk of recurrence in the post-renal transplant period and an improvement after any lymphoproliferative treatment [19]. It is therefore crucial to correctly distinguish between patients with MGUS and CKD from other causes, and patients with CKD due to renal involvement in the course of MGRS in order to use pre-transplant-specific therapies to target the responsible clone and possibly achieve a complete remission of the haematological disorder.

Based on the high recurrence risk reported in literature, as policy at our Centre, patients with MGUS of renal significance that determined the cause of ESRD are not eligible for KT unless they reached a stable remission of the haematological disease [20–23]. None of the cases described in the present work had MGRS; however, ∼30% of them had an unknown diagnosis of

Table 2. Clinical and functional characteristics in patients with pre-transplant MGUS versus controls

Clinical variables	MGUS ($n = 65$)	Controls ($n = 1079$)	P-value
Follow-up, median, years	3.5 (0–14)	8.3 (0–14.9)	NS
sCr, median, mg/dL			
At discharge (n)	1.9 (0.87–7.5) (64)	1.8 (0.5–8.1) (1038)	NS
1 year (n)	1.6 (0.8–4.3) (57)	1.5 (0.6–6.5) (989)	NS
2 years (n)	1.6 (0.7–4.6) (54)	1.5 (0.2–4.6) (943)	NS
5 years (n)	1.6 (0.8–3) (29)	1.5 (0.6–5.9) (744)	NS
10 years (n)	1.6 (1–3) (10)	1.4 (0.5–5.1) (267)	NS
Last follow-up (n)	1.8 (0.7–9) (61)	1.7 (0–11.9) (1015)	NS
Pto, median, g/24 h			
At discharge (n)	0.3 (0.1–3) (61)	0.36 (0–12) (970)	NS
1 year (n)	0.2 (0–4) (57)	0.2 (0–8.3) (949)	NS
2 years (n)	0.2 (0–3.9) (53)	0.2 (0–10) (911)	NS
5 years (n)	0.3 (0–2) (29)	0.2 (0–10) (727)	NS
10 years (n)	0.3 (0.1–3.8) (10)	0.2 (0–18) (262)	NS
Last follow-up (n)	0.3 (0–4.2) (57)	0.3 (0–18) (940)	NS
Functioning grafts at the end of the follow-up, n (%)	56 (86.2)	851 (78.9)	NS
Deaths, n (%)	7 (10.8)	204 (18.9)	NS
Allograft rejection, n (%)	6 (9.3)	168 (15.6)	NS
Cellular rejection, n (%)	2 (3.1)	81 (7.5)	NS
Vascular rejection, n (%)	2 (3.1)	47 (4.4)	NS
Cellular + vascular rejection, n (%)	2 (3.1)	40 (3.7)	NS
Infectious complications, n (%)	38 (58.7)	753 (69.8)	<0.05
Post-KT neoplasia, n (%)	12 (18.5)	234 (21.7)	NS
mTOR inhibitor during follow-up, n (%)	20 (30.3)	159 (14.7)	<0.05

Table 3. Laboratory evaluations in MGUS patients during follow-up

Laboratory findings	Diagnosis ($n = 65$)	Discharge ($n = 65$)	First year ($n = 57$)	Second year ($n = 54$)	Fifth year ($n = 29$)	Tenth year ($n = 10$)
Monoclonal peak						
Present/absent, n	65/0	10/12	24 /13	19/12	9/9	4/5
NA, n	0	43	20	23	11	1
Seric immunofixation						
Positive/negative, n	51/9[a]	9/8	17/5	16/6	11/5	3/1
NA, n	5	48	35	32	13	6
Urinary immunofixation						
Positive/negative, n	16/30	1/16	4/13	2/17	1/13	0/4
NA, n	19	48	40	35	15	6
kappa/lambda ratio						
Increased, n	10	2	2	1	0	0
Reduced, n	2	0	0	0	1	1
Normal, n	10	5	7	8	6	3
NA, n	43	58	48	45	22	6
IgG MGUS, n	43	43	35	34	17	5
IgA/IgM reduction, n	13	11	2	0	0	0
NA, n	8	21	28	23	11	4
IgA MGUS, n	6	6	6	5	2	0
IgG/IgM reduction, n	1	0	0	0	0	0
NA, n	1	5	5	4	1	0
IgM MGUS	3	3	3	2	2	2
IgG/IgA reduction, n	1	2	1	0	0	0
NA, n	0	1	2	1	1	1

[a]Intended as first immunofixation test available with persistence of monoclonal peak in several electrophoresis.
NA: not available

ESRD, therefore it may not be possible to unequivocally exclude the presence of MGUS of renal significance in some of our patients. However, no recurrence of renal disease on the grafted kidneys was recorded and this further argues against the possible role of the coexisting MGUS on the development of renal damages.

For patients with MGUS lacking any clear correlation between monoclonal gammopathy and renal failure, specific and

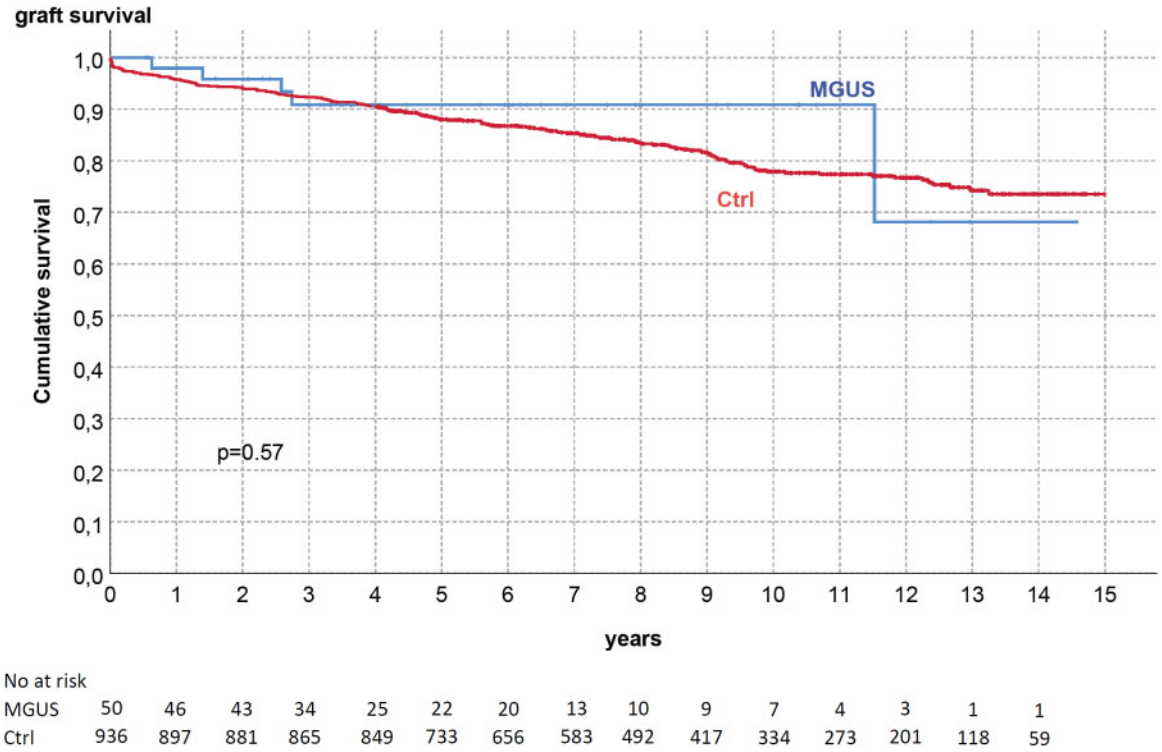

FIGURE 1: Death-censored survival from the time of KT of patients with MGUS and matched population with a negative history (controls). No significant difference in survival was noted (P = 0.574).

univocal recommendations or contraindications to perform KT have not been established so far. Both the 2005 Canadian Society Guidelines and the 2013 Caring for Australians with Renal Impairment (CARI) Guidelines on recipient assessment for KT did not recommend a specific waiting time for patients with pre-existing MGUS [7, 8]. The European Renal Best Practice Guidelines only focused on previous lymphomas without recommendations about other oncohaematological conditions [10]. The 2011 British Transplantation Society Guidelines focused instead on previous post-transplant lymphoproliferative disease (PTLD) [12]. Furthermore, no guideline contains indications about examinations needed before KT to assess disease remission or non-progression in case of MGUS. Additional specific tests are usually performed only in selected cases and when a haematological consultation is requested. Indeed, also in our series, only 39.4% of our MGUS patients underwent a deep examination including BM biopsy before KT. Thus, given the increasingly documented presence of MGUS in the general population and consequently in subjects requiring KT, as also confirmed by our survey, specific recommendations for the management of these patients in the setting of solid organ transplant are warranted.

The significant higher prevalence of previous KT in cases (23% versus 13.3%, $P < 0.05$) could be partly related to the high prevalence of patients with MGUS developed after their first KT (11/15). The incidence of MGUS after KT has been assessed in few studies, with conflicting results: Passweg *et al.* showed a 5-year cumulative incidence of 10.7%, much higher than expected for a group of similar age from the general population [24], Cuéllar-Garcia *et al.* reported a 2.9% prevalence of the haematologic disease after KT [25], while Bancu *et al.* only a 1.57% prevalence [5], and Alfano *et al.* found an overall prevalence of patients with stable MGUS after KT of 8.1% [26]. In these studies, KT and its associated need for immunosuppressive therapies seemed to act as predisposing factors for the development of MGUS irrespective of patient's age and gender.

Besides a few case reports and case series, there are limited data in the literature regarding the long-term outcome of patients with oncohaematological disease undergoing KT. Our study offers insights on MGUS, with the observation in a significant group of 65 patients with pre-existing MGUS and treated with KT for ESRD. In the general population, MGUS has reportedly a low progression rate, around 1–1.5%/year [15]. In our series, no patient showed a disease progression after KT, regardless of the immunosuppression prophylaxis after KT and type or concentration of serum monoclonal protein. Conflicting results are reported in the literature. In particular, 4 out of 23 (17.4%) patients with pre-transplant MGUS developed post-transplant smoldering MM and PTLD in the study by Naina *et al.* [3], whereas in two other small series (nine patients each) with pre-existing MGUS, only one post-transplant MM has been reported [4, 5]. Lastly, a case report described the occurrence of AL amyloidosis 10 years after KT and prolonged over-immunosuppression in a patient with pre-existing MGUS [6]. All authors concluded that patients with MGUS and ESRD should not be excluded from KT, although a close post-transplant monitoring is clearly recommended. However, no specific indications have been so far outlined regarding type and timing of diagnostic examinations to be performed before and at given intervals following KT.

A second issue of concern is the possible negative influence of the co-existing of MGUS on transplant outcomes. Indeed, our matched cohort study showed no differences in graft and patient survival between MGUS group and controls, as also

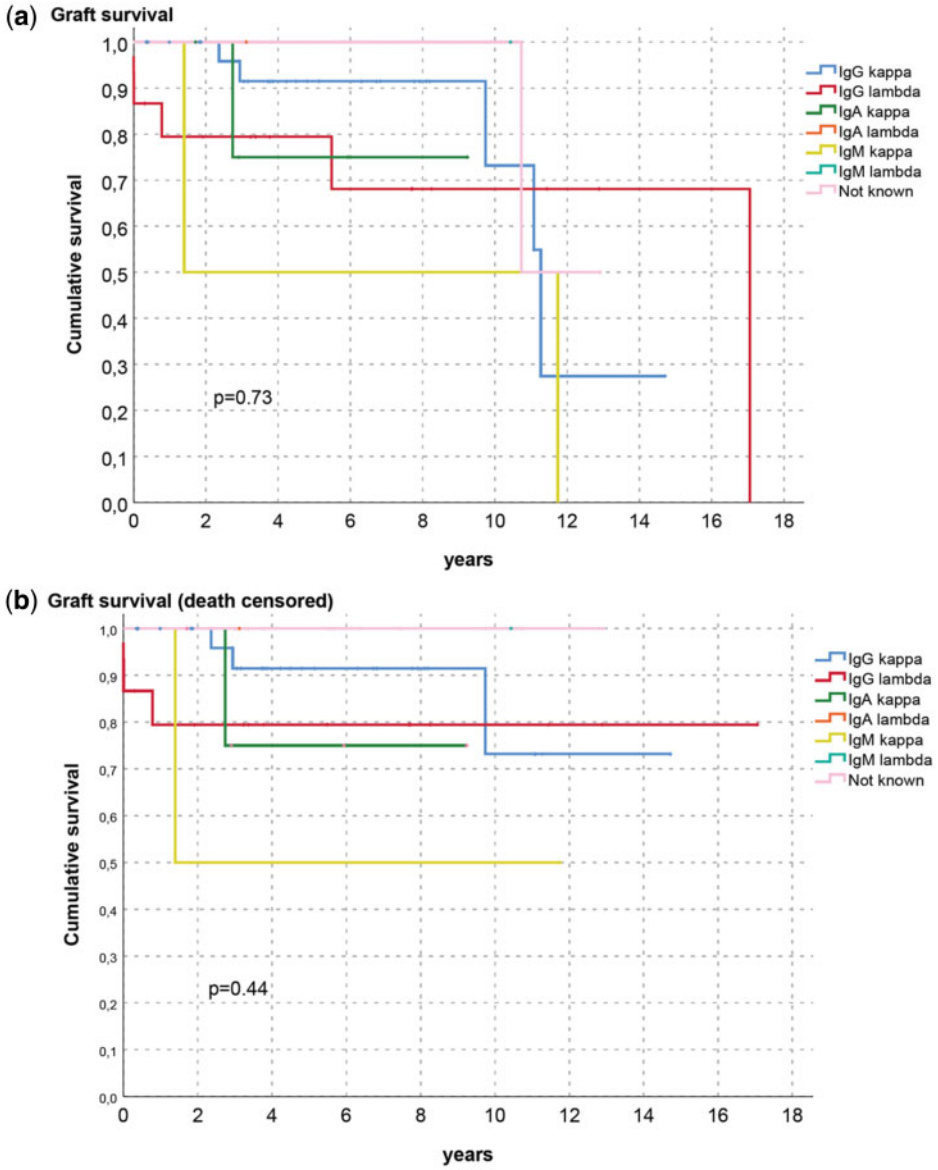

FIGURE 2: Overall survival (**a**) and death-censored survival (**b**) from the time of KT according to MGUS isotypes. No significant difference in survival was noted (P = 0.731 and 0.44, respectively).

confirmed by the adjunctive analysis only considering the selected cohort of controls matched for recipient age, gender, number of transplantation and transplant period. Furthermore, incidence of main post-transplant complications was analogous between the two groups. An increased use of mTOR inhibitors as immunosuppressant therapy was seen in our MGUS series compared with controls (30.3% versus 14.7%, respectively). This can be simply explained by the cautiously use of strong immunosuppressive drugs, as also reflected by the lower infectious complications in the MGUS compared with the control group (56.1% versus 69.8%). Moreover, the anti-proliferative effect of mTOR inhibitors is well known and various studies support its use in the context of post-transplant solid neoplasia, in particular non-melanoma skin cancer. However, evidence favouring the use of mTOR inhibitors in oncohaematological disorders, specifically in co-existing MGUS, are limited [27, 28]. Indeed, specific recommendations on the ideal immunosuppressive regimens to be used in patients with MGUS or other haematological disorders at potentially increased risk of post-transplant complications are lacking. Patients with pre-transplant MGUS are likely to require specific immunosuppressive treatment, both in induction and in maintenance. Large registry-based studies will allow definition of the optimal immunosuppressive strategy for MGUS and other haematological disorders coexisting in patient candidates to KT for ESRD.

In summary, this study addresses the issue of the coexistence of haematological abnormalities, namely the MGUS disorders, in patients undergoing KT for ESRD. To our knowledge, this is indeed the largest series reporting KT and haematological outcomes in patients with pre-transplant MGUS, including a comparative analysis with a control population with similar characteristics and post-transplant management. The study confirms the importance of specific and multidisciplinary approaches for the management of patients with co-existing

haematological abnormalities and ESRD. Moreover, our observations give further support to the concept that patients with pre-existing MGUS may undergo KT, without significantly increased risks of complications, provided that appropriate diagnostic procedures are carefully followed. Additional multidisciplinary studies will help to standardize pre- and post-transplant monitoring protocols for the best management of patients with coexisting MGUS and need of KT.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

R.C. and C.T. contributed to concept design, analysis and interpretation, critical revision and drafting the article; R.G., M.C.T., E.G. and A.L. contributed to data collection and critical revision; F.F. performed statistics; analysis and interpretation, and drafting the article were done by A.M.; C.D. was involved in critical revision; L.B. contributed to concept design, analysis and interpretation, critical revision and drafting the article.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, except in abstract form. All the authors declare that they have no competing interests.

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