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Kidney Transplantation in Patients With MGRS-Associated Lesions: A Case Series

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Abstract

Rationale & Objective: Data on kidney transplantation (KTx) outcomes among patients with monoclonal gammopathy of renal significance (MGRS) are lacking.

Study Design: Case series of patients with MGRS, some of whom received clone-directed therapies prior to KTx.

Setting & Participants: Thirty patients who underwent KTx from 1987 through 2016 after diagnosis with MGRS-associated lesions including light chain deposition disease (LCDD), C3-glomerulopathy with monoclonal gammopathy (C3G-MG), and light chain proximal tubulopathy (LCPT).

Findings: Of the 19 patients with LCDD, 10 were treated prior to KTx while 9 were treatment-naive. Among the treated LCDD patients, 3 (30%) experienced histologic recurrence, 2 (20%) developed graft failure, and 2 (20%) had mortality during median follow-up of 70 (3–162) months

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after KTx. In the treatment-naive LCDD group, 8 (89%) had histologic recurrence, 6 (67%) grafts failed, and 4 (44%) patients died, during the median follow-up of 60 (35–117) months. Of the 5 patients who achieved complete response (CR) prior to KTx, none died, and only 1 had experienced graft failure 162 months after the KTx. Three of 5 patients with C3G-MG were treatment-naive prior to KTx. Both of the patients who were treated before KTx had histologic recurrence, 1 developed graft failure and 1 died. Among the 3 treatment-naive C3G-MG patients, histologic recurrence occurred in all, while graft loss and mortality were observed in 2, and 1 patients, respectively. In the LCPT group (n=4), histologic recurrence was noted in all 3 patients who did not receive clone-directed therapies before KTx, and 2 of these patients died, 1 with a functioning kidney. The only patient with LCPT who received therapy prior to KTx did not have histologic recurrence, graft loss, or mortality.

Limitations: Small sample size, non-standardized managements, retrospective design.

Conclusions: Recurrence is very common in all MGRS-associated lesions after KTx. Achieving a complete hematologic response may reduce the risk of recurrence, graft loss, and mortality. More studies are needed to determine effects of hematologic response on outcomes in each MGRS-associated lesion.

Summary

Data on kidney transplantation (KTx) in patients with an MGRS-associated kidney disease is limited due to the risk of recurrence that had discouraged KTx in these patients. This study reports on a single center experience of these patients with and without pretreatment of the MGRS prior to KTx. Recurrence was much more common in patients who did not receive treatment for MGRS prior to KTx. Histologic recurrence was often responsible for graft loss and hematologic relapse/progression was frequently the cause of death in these patients. Achieving a CR prior to KTx appeared to reduce the risk of recurrence/relapse and possibly improve overall survival. Treatment of the MGRS seemed to stabilize allograft function in many of those who relapsed, but allograft losses and deaths still occurred despite hematologic response. Outcomes of MGRS after KTx are heterogeneous and more studies are needed to determine the optimal hematologic response before proceeding to KTx and to identify optimal treatment of recurrences.

Keywords

monoclonal gammopathy; transplantation

Introduction

Our understanding of kidney disease related to plasma cell disorders is rapidly evolving.[1,2] This is due in large part to the advances in diagnostic techniques,[3] and detection methods of monoclonal proteins.[4–6] Although monoclonal proteins had been recognized to be nephrotoxic,[7] the acknowledgement that they can cause kidney injury in the absence of a hematologic malignancy has only been recently proposed.[8] These monoclonal gammopathies are now classified as monoclonal gammopathy of renal significance (MGRS).[8] The recent consensus report by the International Kidney and Monoclonal Gammopathy Research Group lists the following lesions as MGRS-associated: immunoglobulin-associated amyloidosis, immunotactoid glomerulonephritis,

cryoglobulinemic glomerulonephritis, light-chain proximal tubulopathy (LCPT), monoclonal immunoglobulin deposition disease, proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID), monoclonal fibrillary glomerulonephritis, C3 glomerulopathy with monoclonal gammopathy (C3G-MG), monoclonal gammopathy-associated thrombotic microangiopathy and miscellaneous disorders that include monoclonal anti-glomerular basement membrane disease and membranous nephropathy due to monoclonal gammopathy.[9]

Monoclonal proteins not only contribute to the progression to end-stage kidney disease (ESKD), but also pose a high risk of recurrent disease after kidney transplantation (KTx). It is important to note that the management of recurrent diseases after KTx requires special attention for a timely diagnosis and treatment.[10–12] Prior to the recognition of MGRS-associated lesions, the results of KTx in patients with light-chain deposition disease (LCDD) were quite discouraging.[13] Outcomes became more favorable after the introduction of clone-directed therapy for MGRS.[14] Several studies of KTx in immunoglobulin light-chain (AL) amyloidosis and PGNMID have recently been published from our institution and others, but data on other MGRS-associated lesions are still lacking.[15–21] This case series included patients who were treated for MGRS prior to KTx as well as patients were treatment-naive. The intent of this paper is to review our experience of KTx of patients with other MGRS-associated lesions, to characterize the outcomes of patients with LCDD, C3G-MG, LCPT, and to describe their impact on patient and kidney allograft outcomes.

METHODS

We reviewed medical records of patients who had ESKD due to MGRS-associated lesions and subsequently underwent KTx between 1987 through 2016. The diagnosis of MGRS-associated lesions was made based on kidney biopsy findings and serum and/or urine monoclonal protein studies. Disease groups included LCDD, C3G-MG, and LCPT. Data were obtained from electronic medical records. We used different combinations of the following terms in order to identify patients with MGRS-associated lesions from pathology reports of kidney allograft biopsies: ‘‘Banff’’, ‘‘monoclonal’’, ‘‘gammopathy’’, ‘‘monoclonal gammopathy of renal significance’’, ‘‘MGRS’’, ‘‘light-chain deposition disease’’, ‘‘LCDD’’, ‘‘monoclonal immunoglobulin deposition disease’’, ‘‘LCDD’’, ‘‘light-chain proximal tubulopathy’’, ‘‘LCPT’’, ‘‘C3-glomerulopathy with monoclonal gammopathy’’. In this study, we have included some patients from previous papers from our institution regarding KTx in LCDD,[13,22], 2 patients with C3-MG [23], and 1 with LCPT.[24] For those who underwent KTx more than once, only the course of the first kidney transplant was described. Our study was exempted from the need for approval by the Mayo Clinic Institutional Review Board due to the retrospective design, confidentiality of patient identity, and absence of any invasive procedures. Informed consent was waived for the same reasons.

All kidney biopsies were processed for light-microscopy, and immunofluorescence analysis, while electron microscopic evaluation was available in all except 2. Protocol allograft biopsies were performed at implantation, 4-months, 1-year, 2-years, 5-years, and 10-years post-transplantation. Histological recurrence was defined as the demonstration of MGRS-

associated lesion in the protocol or clinically indicated allograft kidney biopsies.[25,26] Assessment of hematologic response was according to the 2016 International Myeloma Working Group (IMWG) uniform response criteria for multiple myeloma,[27] and consensus guidelines for hematologic responses and progression criteria for immunoglobulin light-chain amyloidosis (The International Society of Amyloidosis [ISA] criteria).[28] These criteria are shown in Table 1. Treatment-naïve cases did not receive clone-directed therapies prior to KTx, due to that their disease was diagnosed years before the definition of MGRS, or a late diagnosis (after the KTx).

Hematologic relapse was defined as the reemergence of the clone or M-protein by immunofixation studies. Histologic recurrence was defined as the detection of recurrent MGRS by allograft kidney biopsies. Clinical relapse was defined as an increase in serum creatinine of ≥0.3 mg/dl (≥26.52 μmol/L) and/or doubling of urinary protein excretion to a level ≥0.5 g/day temporally related to hematologic relapse or histological recurrence which could not be explained by other factors. Graft failure was defined as the permanent loss of kidney function and need for renal-replacement therapy (dialysis or re-transplantation). Acute rejection was defined and graded according to Banff criteria that was current at the time of biopsy interpretation.[29]

Quantitative variables were expressed as median (range, minimum-maximum). Qualitative variables were expressed as proportions. Statistical analysis was performed using STATA version 13.0 (*Stata* Corporation, College Station, TX, USA).

RESULTS

The cohort consisted of 30 kidney transplants that included 19 LCDD (n=19), C3G-MG (n=5), and LCPT (n=4). In the LCDD group, 9 patients were treatment-naive prior to KTx while the remaining 10 received some therapy for the MGRS before KTx. Three of the 5 patients with C3G-MG treatment-naive while Only 1 of 4 patients with LCPT received treatment for MGRS prior to KTx. Baseline patient characteristics are given for each MGRS-associated lesion in Table 2.

Monoclonal Immunoglobulin Deposition Disease

Native kidney histology confirmed the diagnosis of LCDD in all 19 patients, of whom 9 (47%) were men and 10 were women (53%), with a median age of 52 (19–66) years. The involved light chain was kappa in 89.5% of cases. Two patients had negative serum protein electrophoresis/serum immunofixation electrophoresis (SPEP/SIFE) and urine protein electrophoresis/serum immunofixation electrophoresis (UPEP/UIFE) and Polyclonality was seen in urine of 2 with negative SPEP/SIFE. In these 4 cases, monoclonality was confirmed by bone marrow and kidney biopsies. The diagnosis of LCDD was made in 3 patients following a recurrence after KTx, and confirmed by a review of their native kidney biopsy. Among the remaining 12, monoclonal gammopathy was evident both in serum and urine in 8 patients, only in serum in 1, and only in urine in 3 patients. Of the 3 patients who received the diagnosis of LCDD after KTx, monoclonal gammopathy was present only in urine in 1, both in serum and urine in 1, while monoclonal proteins were not found in SIFE/UIFE in

the other. Bone marrow biopsy showed ≥10% of plasma cells in 3 patients, <10% in 13 and normal in 2 patients. Bone marrow biopsy was not done in 1 case at the time of diagnosis.

Among the 10 patients who received treatment prior to KTx, hematologic responses according to IMWG were: 2 sCR, 3 CR, 4 PR, 1 not applicable (due to unavailable sFLC assay at that time, and negative baseline immunofixation studies). Based on the ISA criteria, 4 were CR, and response category was not applicable to 6 due to the unavailable sFLC assay at that time. Clone-detection and paraprotein studies of patients with LCDD are shown in Table 3.

Recurrence occurred in 8 of 9 LCDD patients who were treatment-naïve prior to KTx at a median 20 (range, 2–33) months post-KTx. One patient did not have recurrence during the follow-up of 49 months. Of the 10 patients who did received treatment prior to KTx, 3 had recurrence at a median 46 (range, 45–76) months after KTx. Two of the 3 patients were treated with (bortezomib-based therapy (n = 1) and lenalidomide-based therapy (n = 1) while 1 did not receive any therapy (before the year 2000). In addition to these 3 histologic recurrences, 2 patients from the pretreated group experienced hematologic relapse. One received melphalan and corticosteroid while the other was treated with ixazomib, venetoclax and corticosteroid.[22]

In the treatment-naive group, 5 of 8 histologic LCDD recurrence episodes were left untreated (all occurred before the year 2000), 4 had graft failure (2 of these experienced mortality later), while 1 died with a functioning kidney. Among the 3 who received therapy for histologic recurrence, 1 achieved CR and enjoyed recurrence-free survival 60 months after KTx and 40 months after histologic recurrence, 1 achieved CR but eventually had graft failure and later died. The last one achieved a VGPR, however, developed graft loss 73 months after the KTx and 22 months after the histologic recurrence. Outcomes of treatments of histologic recurrences and hematologic relapses are shown in Figure 1a while outcomes of patients without recurrence or relapse are presented in Figure 1b.

Overall, graft failure occurred in 8 (42.1%) LCDD patients at a median of 54 months (range, 3–162) after KTx and 15 (2–90) months after histological recurrence. During the median follow-up of 70 (3–162) months after KTx, graft failure occurred in 2 out of 10 patients who received treatment for MGRS prior to KTx, 61 and 162 months after KTx, and both were due to recurrent LCDD. The median follow-up of the treatment-naive group after KTx was 60 (35–117) months, and 6 patients had graft loss at 41 (3–107) months after KTx. Recurrence was the main cause of graft loss in 4 and was deemed to significantly contribute to graft failure in the remaining 2 along with acute rejection.

In total, 6 (31.6%) patients died after KTx at a median of 55 (3–117) months after KTx. Causes of death were hematologic progression or complications of treatment of relapse (n=5), and acute leukemia (n=1). Mortality occured in 2 of 10 patients who were treated for MGRS before KTx, and 4 of 9 who were treatment-naive. Of note, no mortality was observed among the 5 patients who achieved a CR (n=2) or stringent CR (n=3) before KTx, and graft loss occurred only in one, 162 months after KTx.

C3-glomerulopathy with Monoclonal Gammopathy

The median age of the 5 patients was 56 (range, 39–73) years and 4 were male (80%). Three of 5 patients with C3G-MG received the diagnosis after KTx following recurrence by reviewing the native kidney biopsy and were treatment-naive. Monoclonal gammopathy was detected in both serum and urine in 2, and only in serum in 1, prior to KTx. The remaining 2 patients who received the diagnosis prior to KTx had IgG kappa and IgG lambda monoclonal gammopathy in both SPEP and UPEP (Table 4). These 2 patients achieved only minimal response from cyclophosphamide, plasma exchange, and/or mycophenolate mofetil pretransplant according to IMWG (ISA not applicable due to unavailable sFLC assay at that time). The diagnosis of C3GN was confirmed by pronase IF in one case, while this was not available in the remaining 4 patients.

Levels of complement C3 and C4 were available in 4 of 5 patients. Two had low serum C3 (33 and 59 mg/dL; normal range 75 – 175mg/dL) and normal serum C4 (17 and 21 mg/dL; normal range 14–40 mg/dL), 1 had normal C3 (80 mg/dL) and low C4 (22 mg/dL) and 1 had normal C3 (87 mg/dL) and C4 (13 mg/dL) levels. Functional complement testing was performed in 2, one of whom had abnormality in alternative pathway, and the other had increased serum membrane attack complex (sMAC). C3 nephritic factor was not tested in any case. One patient had one copy of variant of unknown significance for complement factor H. None of the patients had mutations in CFH, CFI, CFB, MCP, C3 or CFHR5.

Recurrence was detected in all of 5 transplants at a median 70 (range, 26–138) days after KTx. All allograft biopsies were clinically indicated at the time of histological recurrence. Three patients progressed from MGRS to multiple myeloma after the KTx. Recurrence occurred at 26 and 138 days after KTx in 2 C3G-MG patients who were treated prior to KTx. In the 3 treatment-naive patients, recurrence occurred at 70, 75, and 126 days post-KTx.

Among the 3 treatment-naive patients, 1 did not receive treatment (year 1987) at the time of recurrence, but was given glucocorticoids for acute rejection with no renal response. Another patient developed hematologic progression and was lost to follow-up. The last treatment-naive case received eculizumab post-KTx during histologic recurrence. Kidney functions was stable following eculizumab but subsequently, patient experienced hematologic progression which did not respond to CyBorD leading to mortality approximately 3 years after histologic recurrence.

In one the 2 patients who received therapy prior to KTx, histologic recurrence was treated with melphalan and autologous stem-cell transplantation (ASCT) with minimal response. Subsequent therapies with thalidomide and bortezomib did not provide a better hematologic response. The graft failed 65 months after the recurrence, and the patient died 85 months after the KTx. The second case initially received rituximab and plasma exchange for histologic recurrence. Later, the patient underwent ASCT, and subsequently received daratumumab plus lenalidomide plus dexamethasone. The patient achieved a stringent CR according to IMWG and did not have relapse, recurrence, graft loss, or mortality during the follow-up of 204 months after KTx. Treatments and outcomes of patients with recurrent C3G-MG are summarized in Figure 2.

Among the 3 treatment-naive cases, graft failure occurred in 2 and mortality was observed in 1 during the median follow-up of 22 (3–37) months. In the 2 patients who received treatment prior to KTx, one did not have graft failure or death during the follow-up of 204 months, while the other one experienced graft failure 65 months after KTx and death 85 months after KTx. Acute rejection episodes were observed in 2 of 3 treatment-naive cases, and 1 of 2 who received therapy prior to KTx, all within the first year following KTx.

Light-Chain Proximal Tubulopathy

Patients with LCPT underwent KTx at the median age of 60 (40–68) years, and 3 of 4 (75%) were female. The diagnosis of LCPT was made after the KTx in the 2 patients, following recurrence in the allograft and by reviewing the native kidney biopsy. At the time of diagnosis, one patient had a monoclonal IgM kappa in serum and monoclonal kappa light chain in urine, while the other had a serum monoclonal IgA kappa while urine studies did not detect any monoclonal proteins (Table 5). In the patients who were diagnosed prior to KTx, one had a monoclonal kappa light chain in both serum and urine while the other had monoclonal kappa only in UIFE. Both patients who were diagnosed prior to KTx had signs of proximal tubular dysfunction including normoglycemic glucosuria, and low-normal serum uric acid and phosphorus levels. BM was performed in 3 patients prior to KTx and plasma cell percentage was reported to be 3%, 4%, and 7% respectively. One patient received lenalidomide-based therapy and subsequently underwent autologous stem-cell transplantation, achieving CR (both by IMWG and ISA criteria) prior to KTx. The remaining 3 were treatment naive.

All treatment-naive cases experienced recurrence at 25 days, 68 days, and 423 days after KTx. One recurrence was captured by protocol biopsy. The patient who achieved CR prior to KTx enjoyed a relapse-free survival with a functioning allograft kidney during the follow-up of 111 months. One graft of a treatment-naive patient failed due to severe (Banff IIB) acute cellular rejection and recurrent disease 5 months after KTx. The patient did not receive any therapy for MGRS to concerns of over-immunosuppression. She died approximately 7 years after the graft failure due to infectious complications. Another treatment-naive patient had hematologic progression at the time of histologic recurrence. The patient achieved a VGPR (both IMWG and ISA) with bortezomib-based therapy and the serum creatinine returned to baseline. One year later, UIFE turned positive, but kidney functions and sFLC were stable. Recurrent LCPT was still evident at the 5-year protocol biopsy. The patient is alive with a functioning kidney allograft after 78 months of follow-up; however, glucosuria never resolved. Recurrence occurred within the first month after KTx in the last patient who was treated with high dose dexamethasone, stem-cell transplantation and plasma exchange respectively. He achieved a VGPR (both IMWG and ISA) with stable serum creatinine, but died 25 months after KTx due to infectious complications. Both of the patients who achieved VGPR following recurrence had ≥10% of plasma cell in bone marrow biopsy at the time of recurrence. All patients had glucosuria at the time of recurrence, which never resolved even in 2 patients who achieved VGPR following recurrence. Treatments and hematologic and renal outcomes of recurrences are shown in Figure 3. At the end of the follow-up, 2 patients died and 2 were alive.

Other post-transplant complications

Seven patients had progression to multiple myeloma (2 LCDD, 3 C3-G, and 2 LCPT) following KTx. Acute cellular rejection was detected in 4 allografts with C3G-MG, 4 allografts of the LCDD group, and 1 allograft with LCPT. One patient developed non-small cell lung cancer and 1 patient had renal-cell carcinoma of the native kidney. Two patients had a diagnosis of myelodysplastic syndrome, one subsequently progressed to acute myelogeneous leukemia and the other died of complications of stem-cell transplant. Two patients had non-melanoma skin cancers. Infectious complications included the following: 2 patients had BK viremia 1 with BK nephropathy, 1 had CMV enteritis, 1 had CMV pneumoniae, 1 had pulmonary nocardiosis, 1 had recurrent urinary tract infection, and 2 patients developed sepsis following bacterial pneumoniae. Overall, 12 patients had mortality. Causes of death were as follows: 5 hematologic progression, 4 infection,1 leukemia, 1 complications of stem-cell transplant, and 1 unknown.

Discussion

The recognition of MGRS-associated lesions has significantly changed the management of these patients who previously were restricted from clone-directed therapy until they met criteria for multiple myeloma or malignant lymphoma. Stabilization and improvement of kidney functions in patients with MGRS-related diseases is now possible due to the ability of clone-directed therapy to achieve the deep hematologic response (generally VGPR or better) required.[14,15,17,30–34] Despite that, some patients can still progress to ESKD. Since MGRS patients typically have long overall survival and KTx for MGRS-associated lesions should be a viable option. However, high rate of recurrence among treatment-naïve patients led to poor outcomes in the past.

In LCDD, recurrence occurred in approximately 80% of patients, prior to the use of clone-directed therapy, which led to graft failure and death.[13,35] In a study of 6 patients who underwent 7 renal transplants for LCDD, the recurrence rate was reduced to 43% by prior treatment that produced a VGPR and only 2 grafts were lost (1 treatment-naive and 1 with no response)[14]. This was similar to another study which reported that both treatment-naive patients lost their graft within 2 years of transplant while 4 patients who achieved a CR had no recurrence up to 9.7 years of follow-up.[33] In the largest series to date, 9 of 23 patients with monoclonal immunoglobulin deposition disease were diagnosed with MGRS during histologic recurrence after the KTx which occurred at a median 32 months (23–42) while recurrence occurred after a median of 38 (32.5–42) months in 4 of 14 patients that achieved a complete response prior to KTx.[36] The majority of graft losses (4 of 5) were observed among treatment-naïve cases, who were diagnosed with MIDD after the KTx. Similar to our case series, recurrence rates were quite high in the treatment-naive LCDD cases which often resulted in graft loss and death due to hematologic relapse or complications of therapy. On the other hand, 5 patients who achieved CR or stringent CR did not experience mortality and only one had graft failure which occurred 162 months after KTx. In this case series, we noted that patients who achieved a CR or better appeared to have few recurrences and experienced good graft survival and overall survival. Our findings will need to be confirmed in larger studies.

The pathogenesis of C3G-MG is unique in that the monoclonal proteins do not cause kidney injury by deposition but rather by interaction with complement regulatory proteins and activation of the complement system, particularly the alternative pathway.[37] In a study from the Mayo Clinic,[37] monoclonal gammopathy was detected in almost one third of patients with C3-glomerulopathy. A large French study revealed the importance of clone-directed therapy in this disease.[38] In this study, only patients who achieved a VGPR or better had a renal response but only patients who received clone-directed therapy were able to achieve a VGPR. All 5 of our cases of C3G-MG had recurrence, and only the patient who achieved a CR after recurrence had favorable renal and overall survival. Anti-complement therapy was prescribed in in in 1 case and stabilized kidney functions. However, the patient had hematologic progression despite CyBorD therapy, which eventually lead to graft failure and mortality. Our series is too small to draw a reliable conclusion. Future studies are needed to determine whether complete hematologic response prior to KTx will be associated with favorable outcomes in patients with C3G-MG and LCPT.

The optimal response required for recurrence prevention could not be determined in this study since only a few cases were available for each subgroup of different MGRS-associated lesions. In addition, although we tried to present both the IMWG and the ISA response criteria, the latter was not applicable in some patients since the ISA criteria mostly rely on serum free light chain assay, which was not available until the early 2000s. In fact, we think that the IMWG criteria may delineate deeper hematologic response better. With the rapid recurrences in some of the MGRS-associated lesions, knowing the exact hematologic response may make the difference between graft lost and no recurrence. Determining this will require larger multicenter studies. Clone-directed therapy may have prevented graft loss in some patients, but the numbers were too low in subgroups for analysis. While more patients remained with a stable kidney function after therapy for recurrence, there were a few who lost the allograft kidney despite the achievement of complete hematologic response.

Our study suggests the time to histologic recurrence is determined by the type of MGRS-associated lesion. It has been shown that each monoclonal protein elicits a specific injury pattern in the kidney.[7] It seems that the type and amount of the monoclonal protein also determines how quickly recurrence occurs after KTx. In our study, treatment-naive LCPT patients had the fastest time to recurrence after KTx (median 68 days). Recurrence in patients with C3G-MG was probably equally as fast (median 75 days) although the numbers were too small to make an accurate comparison. The median time for PGNMID was noted to be 5.5 months from our previous study.[21] The median time to recurrence in the treatment-naïve LCDD allografts was 20 (range, 2–33) months. The risk of recurrence was lower and recurrence took the longest in AL amyloidosis. This may explain why patients with AL amyloidosis can undergo treatment of the MGRS before or after KTx and achieve similar outcomes.[15,17]

Protocol biopsies were instrumental in detecting histologic recurrence often while it was still subclinical. Given how fast graft loss can occur in these patients, early detection may be essential for graft savage. In this study, histologic and clinical recurrence were prevented 3 patients with MIDD who were treated prior to histologic recurrence. Early treatment also

lengthened the time between histologic recurrence and graft loss, particularly in patients with MIDD. The timing of protocol biopsies may need to be individualized for each MGRS-associated lesion, since the median time to recurrence differed significantly among various lesions.

Heterogeneity between management of old and recent cases, low sample size for each group, and retrospective design are important limitations of this case series. ISA response criteria were not applicable to patients who underwent KTx prior to early 2000s due to the unavailability of sFLC assay at that time. A considerable number of cases were managed years before the recognition of MGRS which makes our population more heterogeneous in terms of their management. Clone-directed therapy was not employed in many patients. Our numbers were too small to determine the best clone-directed therapy option.

In conclusion, we demonstrated that recurrence is nearly universal in these MGRS-associated lesions especially when left untreated prior to KTx. Achievement of a complete hematologic response prior to KTx may improve major outcomes. Larger studies to determine the optimal hematologic response will help manage these patients after KTx and make KTx more durable and accessible for these patients.

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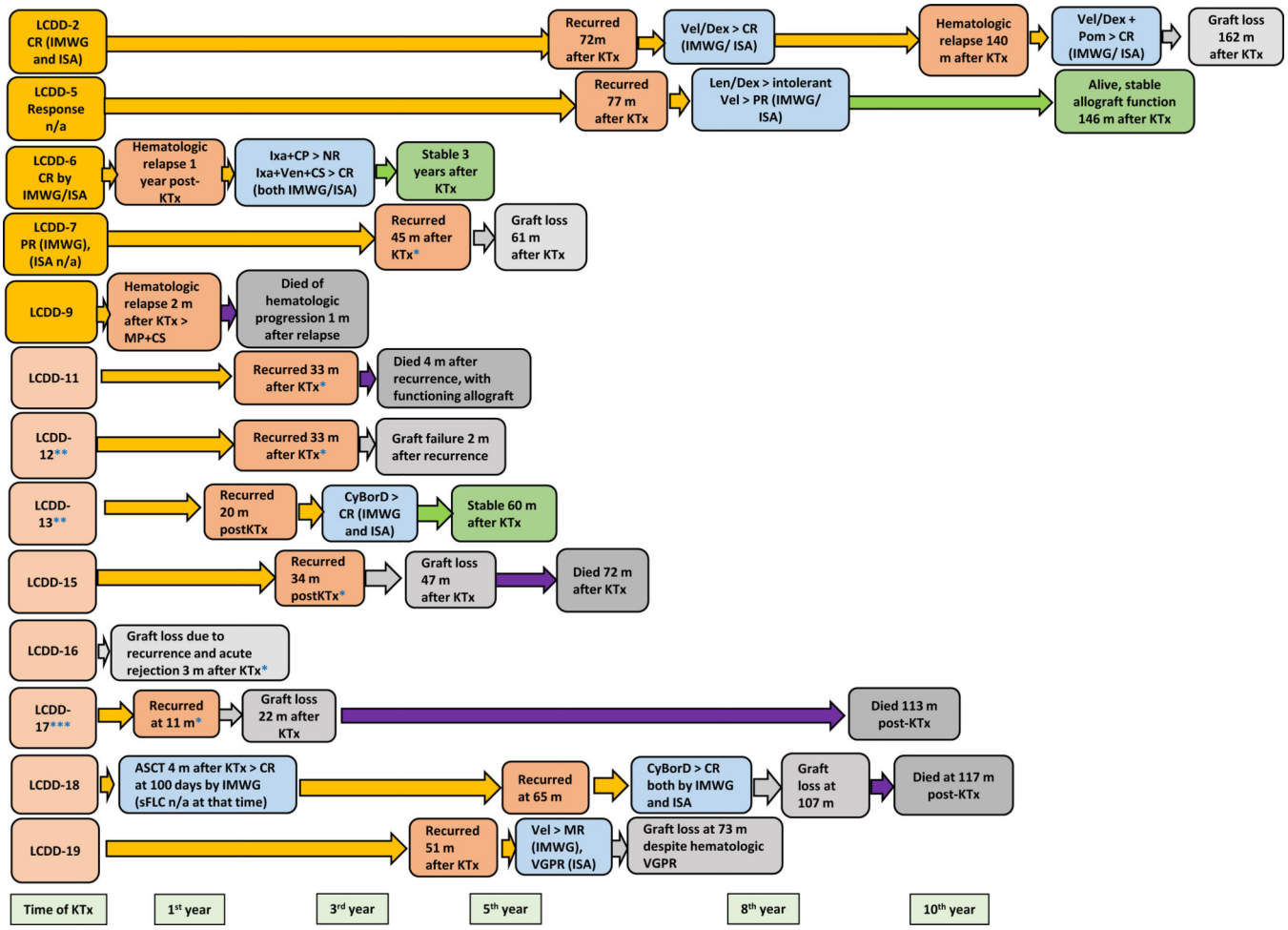

Figure 1a.

Treatment and outcomes of histologic recurrence and hematologic relapse episodes of patients with light chain deposition disease (LCDD). At the time of kidney transplantation (left side of the timeline), pink boxes indicate treatment-naïve cases at baseline, while patients in yellow boxes at baseline received clone-directed therapy prior to kidney transplant. Identification numbers of each case is the same with that given in Table 3. *LCDD-7, LCDD-11, LCDD-12, LCDD-15, LCDD-16 and LCDD-17 did not receive clone-directed therapy for histologic recurrence, these recurrence episodes occurred before the year 2000. **Diagnosis of LCDD in patients with LCDD-12 and LCDD-13 was made after KTx, during recurrence, by reviewing native kidney biopsy. ***2/3 graft nephrectomy was performed to LCDD-17, 1 month after the kidney transplantation, due to thrombosis. ASCT: autologous stem-cell transplantation; CP: cyclophosphamide; CR: complete response; CyBorD: Cyclophosphamide+Bortezomib+Dexamethasone; Dex: dexamethasone; IMWG: International Monoclonal Gammopathy Working Group; ISA: International Society of Amyloidosis; Ixa: ixazomib; KTx: kidney transplantation; Len: lenalidomide; m: months; MDS: myelodysplastic syndrome; MP: melphalan; MR: minimal response; n/a: not applicable; NR: no response; Pom: pomalidomide; PR: partial response;

Pred: prednisone; sFLC: serum free light chain; Vel: bortezomib; Ven: venetoclax; VGPR: very good partial response.

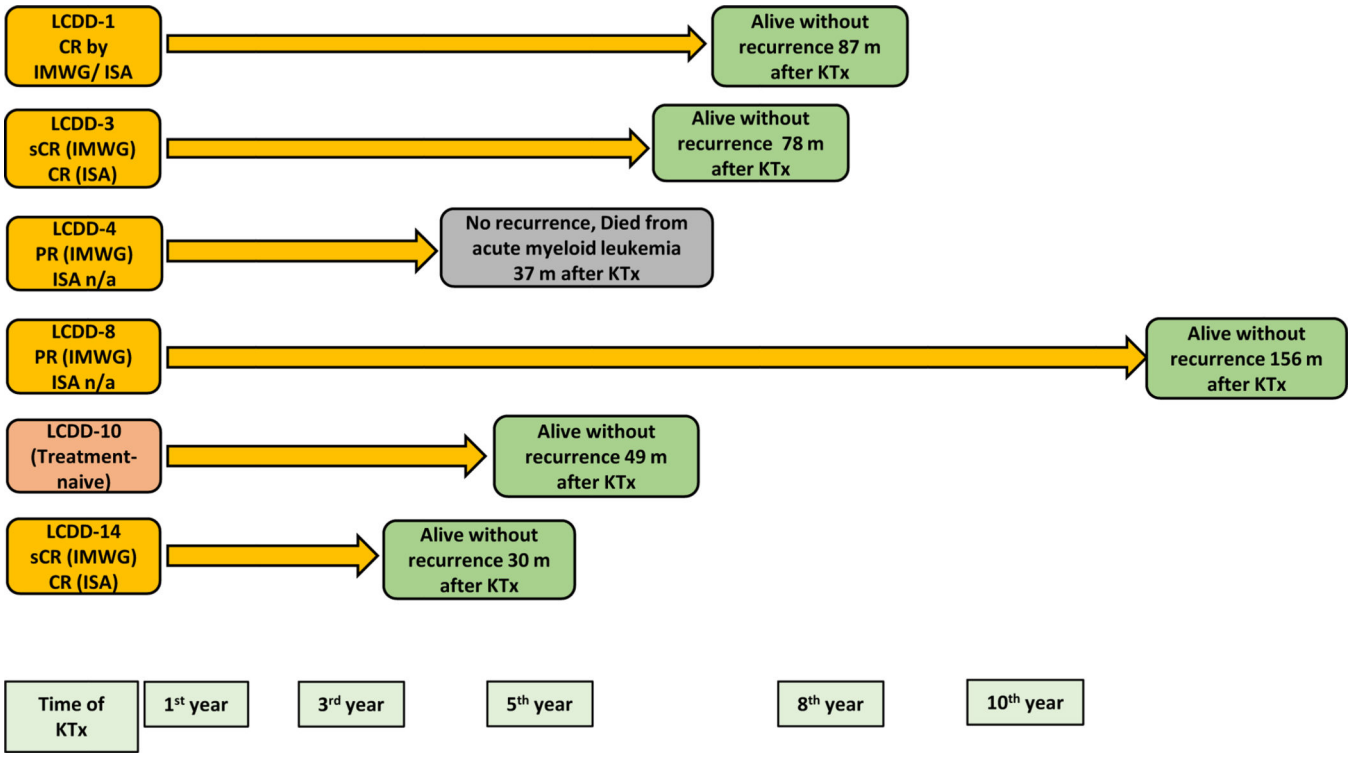

Figure 1b.

Follow-up of patients with light chain deposition disease (LCDD) who did not develop histologic recurrence or hematologic relapse after kidney transplant. At the time of kidney transplantation (left side of the timeline), pink boxes indicate treatment-naïve cases at baseline, while patients in yellow boxes at baseline received clone-directed therapy prior to kidney transplant. Identification numbers of each case is the same with that given in Table 3. CR: complete response; IMWG: International Monoclonal Gammopathy Working Group; ISA: International Society of Amyloidosis; KTx: kidney transplantation; n/a: not applicable; PR: partial response; sCR: stringent CR.

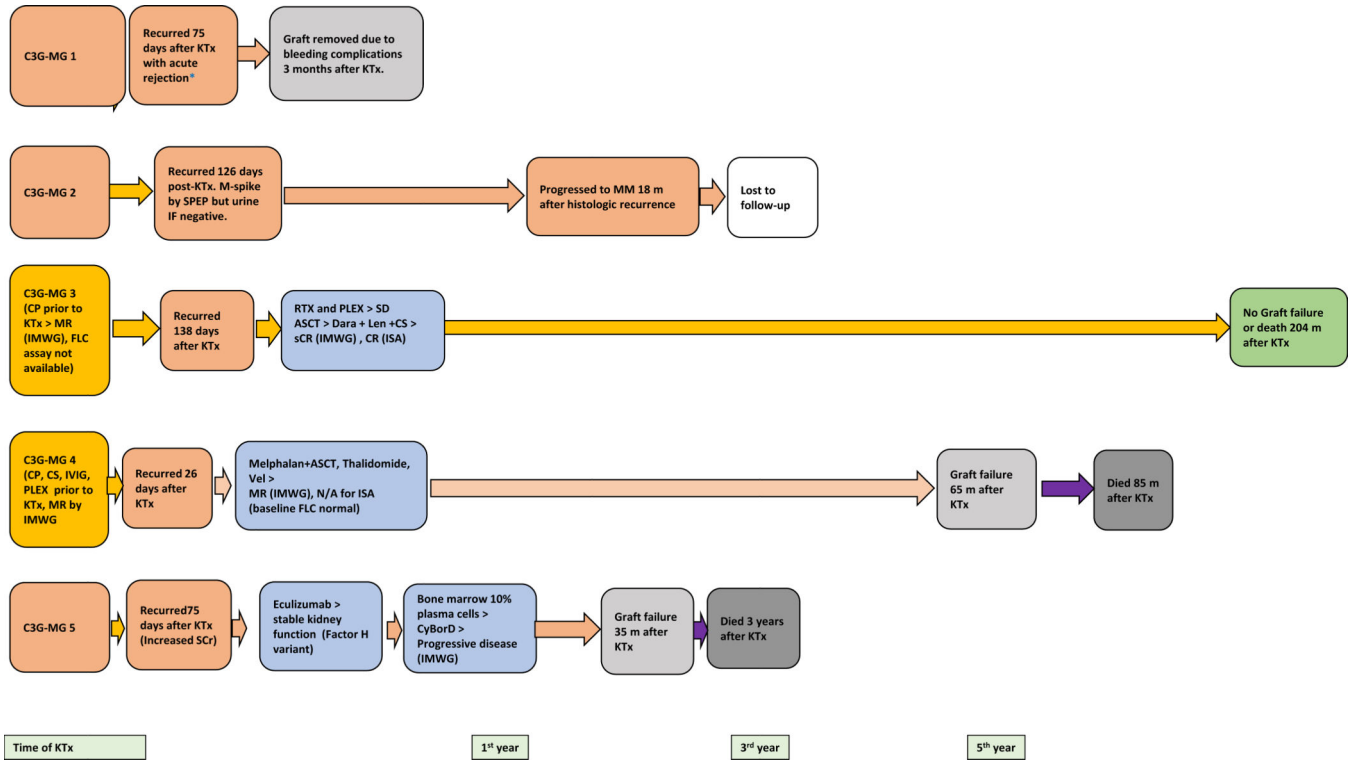

Figure 2.

Treatments of histologic recurrence and hematologic relapse episodes of patients with C3-glomerulopathy with monoclonal gammopathy (C3G-MG) after kidney transplantation. At the time of kidney transplantation (left side of the timeline), pink boxes indicate treatment-naïve cases at baseline, while patients in yellow boxes at baseline received clone-directed therapy prior to kidney transplant. Identification numbers of each case is the same with that given in Table 4. *C3G-MG-1 did not receive clone-directed therapy for histologic recurrence, which occurred in year 1987. CP: cyclophosphamide; CR: complete response; CyBorD: Cyclophosphamide+Bortezomib+Dexamethasone; Dara: daratumumab; Dex: dexamethasone; IMWG: International Monoclonal Gammopathy Working Group; ISA: International Society of Amyloidosis; KTx: kidney transplantation; Len: lenalidomide; MM: multiple myeloma; MP: melphalan; MR: minimal response; N/A: not applicable; PLEX: plasma exchange; PR: partial response; RTX: rituximab; SCr: serum creatinine; sCR: stringent complete response; sFLC: serum free light chain; UPR: urinary protein excretion; Vel: bortezomib.

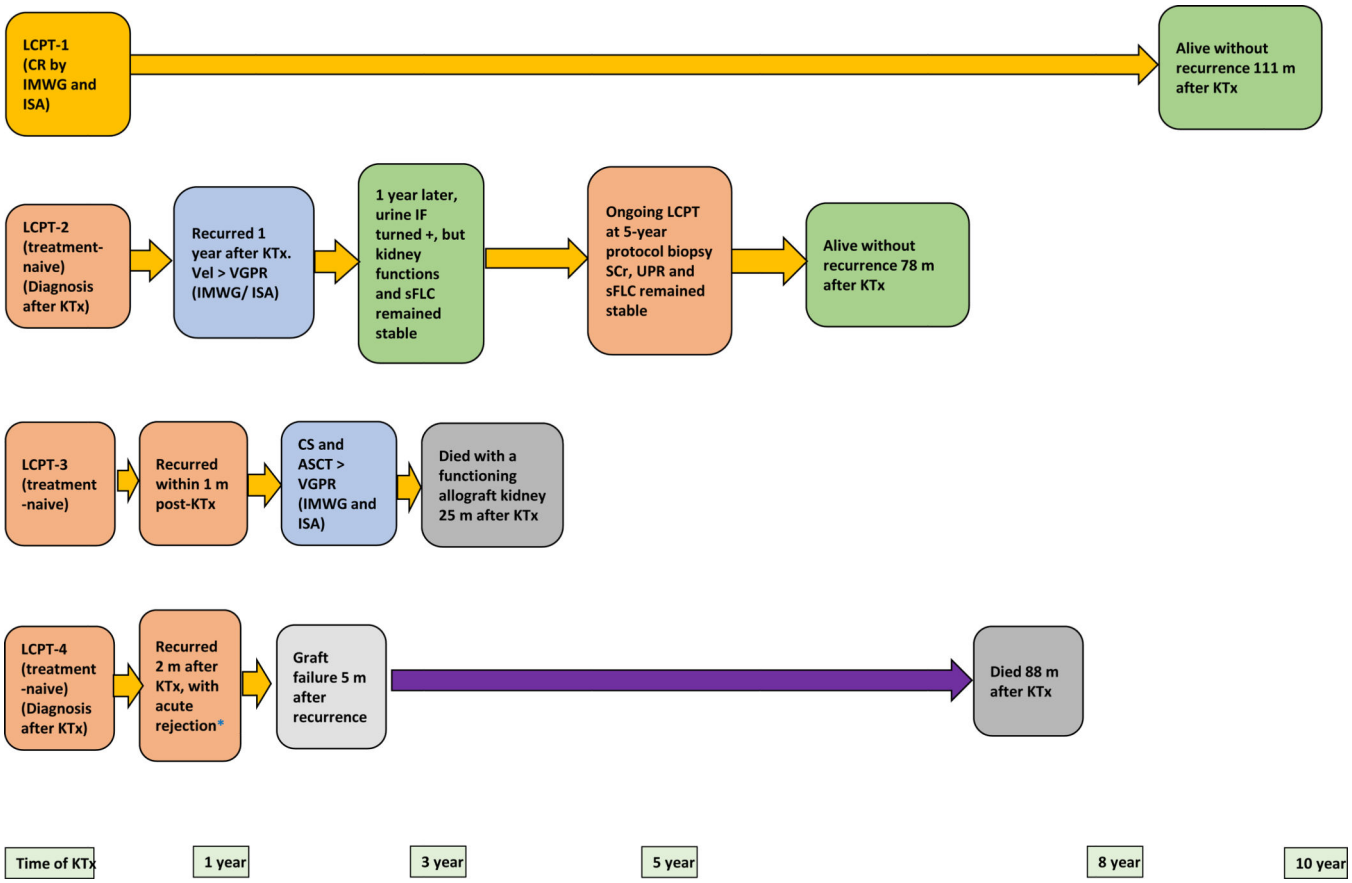

Figure 3.

Post-kidney transplant outcomes of patients with light chain proximal tubulopathy (LCPT) after kidney transplantation. At the time of kidney transplantation (left side of the timeline), pink boxes indicate treatment-naïve cases at baseline, while patients in yellow boxes at baseline received clone-directed therapy prior to kidney transplant. Identification numbers of each case is the same with that given in Table 5. *LCPT-4 was not treated with clone-directed therapy for histologic recurrence but received glucocorticoids for borderline rejection. ASCT: autologous stem-cell Transplantation; Dex: dexamethasone; IMWG: International Monoclonal Gammopathy Working Group; ISA: International Society of Amyloidosis; KTx: kidney transplantation; sFLC: serum free light chain; Vel: bortezomib; VGPR: very good partial response.

Table 1.

The International Myeloma Working Group (IMWG) Criteria for assessment of hematologic response in patients with multiple myeloma, and International Society of Amyloidosis (ISA) criteria for assessment of hematologic response in patients with immunoglobulin light chain amyloidosis

IMWG criteria	
Response category	Criteria
Stringent complete response (sCR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas, and normal free light-chain ratio, and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.
Complete response (CR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas, and ≤5% plasma cells in bone marrow.
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 hours.
Partial response (PR)	≥50% reduction of serum M-protein and reduction in 24-hours urinary M-protein by ≥90% or to <200 mg/24 hours. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference of between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein and serum FLC assays are unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%.
Stable disease	Not meeting the above criteria or the criteria of progressive disease.
ISA criteria	
Response category	Criteria
Complete	Normalization of the free light chain levels and ratio, negative serum and urine immunofixation
Very good partial	Reduction in the dFLC to 40 mg/L
Partial	A greater than 50% reduction in the dFLC
No response	Less than a PR
Progression	From CR, any detectable monoclonal protein or abnormal free light chain ratio (light chain must double) From PR, 50% increase in serum M protein to >0.5 g/dL or 50% increase of M protein to >200 mg/day (a visible peak must be present) Free light chain increase of 50% to >100 mg/L

FLC: free light chain; dFLC: difference between involved FLC and uninvolved FLC; PR: partial response; CR: complete response.

Table 2.

Baseline characteristics of patients with different types of monoclonal gammopathy of renal significance

Variables	LCDD (n=19)	C3-glom (n=5)	LCPT (n=4)
Age, years, median	52 (19–66)	56 (39–73)	60 (40–68)
Male sex, n, %	9 (47)	4 (80)	1 (25)
Serum free light-chain, n, %			
kappa	17 (90)	3 (60)	4 (100)
lambda	2 (15)	2 (40)	0 (0)
Pretransplant treatments, n, %[a]			
None	9 (47)	3 (60)	3 (75)
Melphalan	6 (32)	0 (0)	0 (0)
Cyclophosphamide[b]	1 (5)	2 (40)	0 (0)
Bortezomib	3 (16)	0 (0)	0 (0)
Lenalidomide	0 (0)	0 (0)	1 (25)
ASCT	4 (21)	0 (0)	0 (0)
Plasma exchange	0 (0)	1 (17)	0 (0)
MMF	0 (0)	1 (17)	0 (0)
Preemptive transplant, n, %	6 (32)	3 (60)	1 (25)
Donor type, n, %			
Living	15 (80)	4 (80)	2 (50)
Deceased	4 (21)	1 (20)	2 (50)
Induction, n, %			
Thymoglobulin	5 (26)	4 (80)	1 (25)
Basiliximab	4 (21)	1 (20)	2 (50)
Alemtuzumab	1 (5)	0 (0)	0 (0)
OKT3	1 (5)	0 (0)	1 (25)
Unknown	8 (42)	0 (0)	0 (0)
Maintenance, n, %			
Tac-MMF-Predn	12 (63)	3 (60)	3 (75)
CsA-MMF-Predn	5 (26)	0 (0)	1 (25)
Bel-MMF-Predn	0 (0)	1 (20)	0 (0)
CsA-AZA-Predn	1 (5)	1 (20)	0 (0)
Steroid-free	1 (5)	0 (0)	0 (0)

[a] Some patients were exposed to more than 1 treatment option and the majority received corticosteriods concurrently.

[b] Cyclophosphamide was given alone or concurrently with bortezomib-based regimen. AZA: azathioprine, Bel: belimumab, CsA: cyclosporine-A, MMF: mycophenolate mofetil, Predn: prednisone, Tac: tacrolimus.

Table 3.

Hematologic studies of patients with light chain deposition disease at important time points.

Patient	Time	sFLC assay (mg/dL)			Serum		Urine		Bone marrow	Hematologic response	
		κ	λ	κ/λ	SPEP	SIFE	UPEP	UIFE	%plasma cells	IMWG	ISA
LCDD-1	Diagnosis	29.1	3.3	8.71	Negative	Negative	Negative	Negative	5%, κ>λ	-	-
	Response	5.98	4.39	1.36	Negative	Negative	Negative	Negative	Normal	CR	CR
	preKTx	4.94	4.57	1.08	Negative	Negative	Negative	Negative	Normal	CR	CR
	postKTx	0.727	0.977	0.744	Negative	Negative	Negative	Negative	ND	-	-
	Final visit	1.37	1.18	1.16	Negative	Negative	Negative	Negative	ND	-	-
LCDD-2	Diagnosis	1.18	1.63	0.72	Negative	Negative	Negative	κ	3–5, κ>λ		
	Response	0.143	0.274	0.52	Negative	Negative	Negative	Negative	ND	CR	CR
	preKTx	0.143	0.274	0.52	Negative	Negative	Negative	Negative	Normal		
	postKTx	0.57	0.31	1.85	Negative	Negative	Negative	Negative	ND		
	Recurrence	1.52	0.746	2.04	Negative	Negative	Negative	κ	3–5%, κ>λ		
	Response	0.21	0.15	1.44	Negative	Negative	Negative	Negative	Normal	CR	CR
	Relapse	5.80	0.739	7.85	Negative	Negative	Negative	κ	3–5%, κ>λ		
	Response	1.75	0.948	1.85	Negative	Negative	Negative	Negative	Normal	CR	CR
	Relapse	1.60	1.20	1.33	Negative	Negative	Negative	κ	ND		
	Response	0.862	0.810	1.02	Negative	Negative	Negative	Negative	ND	CR	CR
	Final visit	0.862	0.810	1.02	Negative	Negative	Negative	Negative	ND		
LCDD-3	Diagnosis	41.9	18.6	2.25	κ	κ	κ	κ	3%, κ>λ	-	-
	Response	2.82	1.65	1.71	Negative	Negative	Negative	Negative	Normal	sCR	CR
	preKTx	5.23	2.88	1.82	Negative	Negative	Negative	Negative	Normal	-	-
	postKTx	1.10	1.09	1.01	Negative	Negative	Negative	Negative	ND	-	-
	Final visit	2.14	3.67	0.58	Negative	Negative	Negative	Negative	-	-	-
LCDD-4	Diagnosis	N/A	N/A	N/A	IgGλ	IgGλ	IgGλ	IgGλ	5–10%, λ>κ		
	Response	N/A	N/A	N/A	IgGλ	IgGλ	IgGλ	IgGλ	ND	PR	N/A
	preKTx	N/A	N/A	N/A	IgGλ	IgGλ	IgGλ	IgGλ	ND		
	postKTx	N/A	N/A	N/A	IgGλ	IgGλ	Negative	Negative	ND		

Patient	Time	sFLC assay (mg/dL)			Serum		Urine		Bone marrow	Hematologic response	
		κ	λ	κ/λ	SPEP	SIFE	UPEP	UIFE	%plasma cells	IMWG	ISA
	Final Visit	N/A	N/A	N/A	IgGλ	IgGλ	Negative	Negative	ND		
LCDD-5	Diagnosis	N/A	N/A	N/A	Negative	Negative	Negative	Negative	5%, κ>λ		
	Response	N/A	N/A	N/A	Negative	Negative	Negative	Negative	<1%	N/A	N/A
	preKTx	N/A	N/A	N/A	Negative	Negative	Negative	Negative	ND	N/A	N/A
	postKTx	N/A	N/A	N/A	Negative	Negative	Negative	Negative	ND	N/A	N/A
	Recurrence	b_{High}	b_{Low}	b_{High}	Negative	Negative	Negative	Negative	ND		
	Response	b_N	b_N	b_N	Negative	Negative	Negative	Negative	ND	PR^b	PR^b
	Final visit	b_N	b_N	b_N	Negative	Negative	Negative	Negative	ND		
LCDD-6	Diagnosis	102	1.74	79.2	Negative	κ	Negative	Negative	10%, κ>λ		
	Response	2.43	2.13	1.14	Negative	Negative	Negative	Negative	<5%, κ>λ	CR	CR
	preKTx	17.4	9.1	1.91	Negative	Negative	Negative	Negative	<5%, κ>λ	CR	CR
	postKTx	6.44	1.44	4.47	Negative	Negative	Negative	Negative	ND		
	Relapse	17.7	1.09	16.2	Negative	Negative	Negative	Negative	ND		
	Response	1.13	1.13	1.0	Negative	Negative	Negative	Negative	ND	CR	CR
	Final visit	1.08	0.91	1.13	Negative	IgMλ	Negative	Negative	ND		
LCDD-7	Diagnosis	N/A	N/A	N/A	κ	κ	IgAκ+κ	IgAκ+κ	10–15%, κ>λ		
	Response1	N/A	N/A	N/A	κ	κ	IgAκ+κ	IgAκ+κ	ND	PR	N/A
	preKTx	N/A	N/A	N/A	κ	κ	IgAκ+κ	IgAκ+κ	ND	PR	N/A
	postKTx	N/A	N/A	N/A	ND	ND	ND	ND	ND		
	Recurrence	N/A	N/A	N/A	κ	κ	IgAκ+κ	IgAκ+κ	ND		
	Final visit	N/A	N/A	N/A	κ	κ	IgAκ+κ	IgAκ+κ	ND		
LCDD-8	Diagnosis	N/A	N/A	N/A	IgAκ	IgAκ	IgAκ+κ	IgAκ+κ	N		
	Response	N/A	N/A	N/A	IgAκ	IgAκ	IgAκ+κ	IgAκ+κ	ND	PR	N/A
	preKTx	N/A	N/A	N/A	IgAκ	IgAκ	IgAκ+κ	IgAκ+κ	N	PR	N/A
	postKTx	N/A	N/A	N/A	IgAκ	IgAκ	IgAκ+κ	IgAκ+κ	ND		
	Final visit	N/A	N/A	N/A	IgAκ	IgAκ	IgAκ+κ	IgAκ+κ	ND		
LCDD-9	Diagnosis	N/A	N/A	N/A	Negative	Negative	Polyclonal	Polyclonal	5%, κ>λ		

Patient	Time	sFLC assay (mg/dL)			Serum		Urine		Bone marrow	Hematologic response	
		κ	λ	κ/λ	SPEP	SIFE	UPEP	UIFE	%plasma cells	IMWG	ISA
	Response	N/A	N/A	N/A	Negative	Negative	Polyclonal	Polyclonal		PR	N/A
	preKTx	N/A	N/A	N/A	Negative	Negative	Polyclonal	Polyclonal	5–10%, **κ>λ**	PR	N/A
	postKTx	N/A	N/A	N/A	ND	ND	ND	ND			
	Relapse	N/A	N/A	N/A	**κ**	**κ**	**κ**	**κ**	>10%, **κ>λ**		
	Response	N/A	N/A	N/A	**κ**	**κ**	**κ**	**κ**	ND	PD	N/A
	Final visit	N/A	N/A	N/A	**κ**	**κ**	**κ**	**κ**	ND		
LCDD-10	Diagnosis	*a*	-	-	-	-	-	-	-		
	preKTx	3.30	60.8	0.05	**λ**	**λ**	**λ**	**λ**	<5%, **λ>κ**	Naive	Naive
	postKTx	1.07	3.05	0.35	ND	ND	ND	ND	ND		
	Final visit	ND	ND	ND	**λ**	**λ**	**λ**	**λ**	ND		
LCDD-11	Diagnosis	N/A	N/A	N/A	**κ**	**κ**	**κ**	**κ**	5–8%, **κ>λ**		
	preKTx	N/A	N/A	N/A	**κ**	**κ**	**κ**	**κ**	ND	Naive	Naive
	postKTx	N/A	N/A	N/A	ND	ND	ND	ND	ND		
	Recurrence	N/A	N/A	N/A	**κ**	**κ**	**κ**	**κ**	ND		
	Final visit	N/A	N/A	N/A	**κ**	**κ**	**κ**	**κ**	ND		
LCDD-12	Diagnosis	-	-	-	-	-	-	-	-		
	preKTx	N/A	N/A	N/A	Negative	Negative	Negative	Negative	5%, **κ>λ**	Naive	Naive
	postKTx	N/A	N/A	N/A	ND	ND	ND	ND	ND		
	Recurrence	N/A	N/A	N/A	Negative	Negative	Negative	Negative	5%, **κ>λ**		
	Final visit	N/A	N/A	N/A	Negative	Negative	Negative	Negative	5%, **κ>λ**		
LCDD-13	Diagnosis	*a*	-	-	-	-	-	-	-	-	-
	preKTx	ND	ND	ND	Negative	Negative	**κ**	**κ**	5%, **κ>λ**	Naive	Naive
	postKTx	19.1	0.79	15.2	Negative	Negative	**κ**	**κ**	-	-	-
	Recurrence	18.7	0.90	20.8	Negative	Negative	**κ**	**κ**	20%, **κ>λ**	-	-
	Response	1.36	1.35	1.01	Negative	Negative	Negative	Negative	<5%, **κ>λ**	CR	CR
	Final visit	2.68	1.17	2.29	Negative	Negative	Negative	Negative	-		
LCDD-14	Diagnosis	103	1.50	68.7	**κ**	**κ**	**κ**	**κ**	10%, **κ>λ**		
	Response	0.776	0.642	1.21	Negative	Negative	Negative	Negative	N	sCR	CR

Patient	Time	sFLC assay (mg/dL)			Serum		Urine		Bone marrow	Hematologic response	
		κ	λ	κ/λ	SPEP	SIFE	UPEP	UIFE	%plasma cells	IMWG	ISA
	preKTx	1.90	1.38	1.38	Negative	Negative	Negative	Negative	ND		
	postKTx	1.41	1.15	1.23	Negative	Negative	Negative	Negative	ND		
	Final visit	1.41	1.15	1.23	Negative	Negative	Negative	Negative	ND		
LCDD-15	Diagnosis	N/A	N/A	N/A	Negative	Negative	Polyclonal	Polyclonal	3–5%, κ>λ		
	preKTx	N/A	N/A	N/A	ND	ND	ND	ND	ND	Naive	Naive
	postKTx	N/A	N/A	N/A	ND	ND	ND	ND	ND		
	Recurrence	N/A	N/A	N/A	Negative	Negative	Polyclonal	Polyclonal	ND		
	Final visit	N/A	N/A	N/A	Negative	Negative	Polyclonal	Polyclonal	ND		
LCDD-16	Diagnosis	N/A	N/A	N/A	Negative	Negative	κ	κ	N		
	preKTx	N/A	N/A	N/A	Negative	Negative	κ	κ	ND	Naive	Naive
	postKTx	N/A	N/A	N/A	ND	ND	ND	ND	ND		
	Recurrence	N/A	N/A	N/A	Negative	Negative	κ	κ	ND		
	Final visit	N/A	N/A	N/A	Negative	Negative	κ	κ	ND		
LCDD-17	Diagnosis	N/A	N/A	N/A	Negative	Negative	κ	κ	5%, κ>λ		
	preKTx	N/A	N/A	N/A	ND	ND	ND	ND	ND	Naive	Naive
	postKTx	N/A	N/A	N/A	ND	ND	ND	ND	ND		
	Recurrence	N/A	N/A	N/A	Negative	Negative	κ	κ	ND		
	Final visit	N/A	N/A	N/A	Negative	Negative	κ	κ	ND		
LCDD-18	Diagnosis	N/A	N/A	N/A	κ	κ	κ	κ	<5%, κ>λ		
	preKTx	N/A	N/A	N/A	κ	κ	κ	κ	8%, κ>λ	Naive	Naive
	postKTx	N/A	N/A	N/A	κ	κ	κ	κ	-		
	preASCT	61.6	1.06	58.1	κ	κ	κ	κ	5%, κ>λ		
	Response	2.06	<0.47	>4.38	Negative	Negative	Negative	Negative	2%, κ>λ	CR	CR
	Recurrence	152	3.49	43.6	Negative	Negative	Negative	κ	ND		
	Response	4.36	3.82	1.14	Negative	Negative	Negative	Negative	Normal	CR	CR
	Final visit	4.36	3.82	1.14	Negative	Negative	Negative	Negative	Normal		
LCDD-19	Diagnosis	N/A	N/A	N/A	IgGκ	IgGκ	Negative	IgGκ	ND		
	preKTx	N/A	N/A	N/A	IgGκ	IgGκ	Negative	IgGκ	ND	Naive	Naive

Patient	Time	sFLC assay (mg/dL)			Serum		Urine		Bone marrow	Hematologic response	
		κ	λ	κ/λ	SPEP	SIFE	UPEP	UIFE	%plasma cells	IMWG	ISA
	postKTx	13.0	1.06	12.3	IgGκ	IgGκ	Negative	IgGκ	ND		
	Recurrence	1.76	0.70	2.51	IgGκ	IgGκ	IgGκ	IgGκ	7%, κ>λ		
	Response	3.04	1.43	2.13	IgGκ	IgGκ	IgGκ	IgGκ	5%, κ>λ	MR	N/A
	Final visit	3.05	0.85	3.58	IgGκ	IgGκ	IgGκ	IgGκ	ND		

[a] The diagnosis was made retrospectively after the kidney transplantation following histological examination of the native kidney biopsy.

[b] The phrases ‘N (normal)’, ‘high’, or ‘low’ denote results obtained from clinical notes and actual results were not available since some of these tests were performed elsewhere. CR: complete response; IMWG: International Monoclonal Gammopathy Working Group; ISA: International Society of Amyloidosis; MM: multiple myeloma; MR: minimal response; N, Normal; N/A: not applicable (Some of the studies were not available due to the unavailability of free light chain assay at that time, or due to the retrospective diagnosis of MGRS after revision of native kidney biopsy); ND: Not done; PCD, plasma-cell dyscrasia; PD: progressive disease; PR: partial response; sCR: stringent complete response; sFLC: serum free light chain; SIFE: serum immunofixation electrophoresis; SPEP: serum protein electrophoresis; UIFE: urine immunofixation electrophoresis; UPEP: urine protein electrophoresis; VGPR: very good partial response.

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Table 4.

Hematologic studies of patients with C3-glomerulopathy with monoclonal gammopathy at important time points.

Patient	Time	sFLC assay (mg/dL)			Serum		Urine		Bone marrow	Hematologic response	
		κ	λ	κ/λ	SPEP	SIFE	UPEP	UIFE	%Plasma cells	IMWG	ISA
C3G-MG 1	Diagnosis[a]	*a*	-	-	-	-	-	-	-		
	preKTx	N/A	N/A	N/A	IgGλ+IgA	IgGλ	IgGλ	IgGλ	Normal	Naive	Naive
	postKTx	Recurrence in the first month, concurrent acute rejection.									
	Recurrence	N/A	N/A	N/A	IgGλ+IgA	IgGλ	IgGλ	IgGλ	ND		
	Final visit	No therapy for recurrence (year 1987), graft loss 1 month after the recurrence. The following 3 allografts failed due to recurrent C3G-MG.									
C3G-MG 2	Diagnosis [a]	*a*	-	-	-	-	-	-	-		
	preKTx	ND	ND	ND	IgGκ	IgGκ	Negative	Negative	3%, κ>λ	Naive	Naive
	postKTx	Recurrence in the first month.									
	Recurrence	ND	ND	ND	IgGκ	IgGκ	Negative	Negative	>10%, κ>λ		
	Response	9.75	1.43	6.82	IgGκ	IgGκ	Negative	Negative	>10%, κ>λ	PD	N/A
	Final visit	9.75	1.43	6.82	IgGκ	IgGκ	Negative	Negative	>10%, κ>λ		
C3G-MG3	Diagnosis	N/A	N/A	N/A	IgGλ	IgGλ	IgGλ	IgGλ	<5%, λ>κ		
	Response	N/A	N/A	N/A	IgGλ	IgGλ	IgGλ	IgGλ	ND	MR	N/A
	preKTx	N/A	N/A	N/A	IgGλ	IgGλ	IgGλ	IgGλ	ND		
	postKTx	N/A	N/A	N/A	IgGλ	IgGλ	IgGλ	IgGλ	ND		
	Recurrence	1	99	0.01	IgGλ	IgGλ	IgGλ	IgGλ	20%, λ>κ		
	Response	UD	UD	UD	Negative	Negative	Negative	Negative	Normal	sCR	CR
	Final visit	UD	UD	UD	Negative	Negative	Negative	Negative	Normal		
C3G-MG4	Diagnosis	2.23	1.39	1.6	IgGκ	IgGκ	IgGκ	IgGκ	5%, κ>λ		
	Response	0.954	0.294	3.24	IgGκ	IgGκ	IgGκ	IgGκ	3%, κ>λ	MR	N/A
	preKTx	0.954	0.294	3.24	IgGκ	IgGκ	IgGκ	IgGκ	3%, κ>λ	MR	N/A
	postKTx	Recurrence in the first month.									
	Recurrence	0.175	0.229	0.176	IgGκ	IgGκ	IgGκ	IgGκ	10%, κ>λ		
	Response	0.19	0.18	1.04	IgGκ	IgGκ	IgGκ	IgGκ	3%, κ>λ	MR	N/A
	Final visit	3.02	0.237	0.02	IgGκ	IgGκ	IgGκ	IgGκ	-		

Patient	Time	sFLC assay (mg/dL)			Serum		Urine		Bone marrow	Hematologic response	
		κ	λ	κ/λ	SPEP	SIFE	UPEP	UIFE	%Plasma cells	IMWG	ISA
C3G-MG5	Diagnosis	*a*	-	-	-	-	-	-	-		
	preKTx	ND	ND	ND	IgGκ	IgGκ	Negative	IgGκ	ND	Naive	Naive
	postKTx	ND	ND	ND	ND	ND	ND	ND	ND		
	Recurrence	3.07	0.73	4.19	IgGκ	IgGκ	Negative	IgGκ	10%, κ>λ		
	Response	11.7	1.34	8,73	IgGκ	IgGκ	Negative	IgGκ	15%, κ>λ	PD	NR
	Final visit	11.7	1.34	8,73	IgGκ	IgGκ	Negative	IgGκ	15%, κ>λ		

[a]The diagnosis was made retrospectively after the kidney transplantation with histological examination of the native kidney biopsy. CR: complete response; IMWG: International Monoclonal Gammopathy Working Group; ISA: International Society of Amyloidosis; MM: multiple myeloma; MR: minimal response; N, Normal; N/A: not applicable (Some of the studies were not available due to the unavailability of free light chain assay at that time, or due to the diagnosis of MGRS in the native kidney after kidney transplantation); ND: Not done; PCD, plasma-cell dyscrasia; PD: progressive disease; PR: partial response; sCR: stringent complete response; sFLC: serum free light chain; SIFE: serum immunofixation electrophoresis; SPEP: serum protein electrophoresis; UD: undetectable; UIFE: urine immunofixation electrophoresis; UPEP: urine protein electrophoresis.

Table 5.

Hematologic studies of patients with light-chain proximal tubulopathy at important time points.

Patient	Time	sFLC assay (mg/dL)			Serum		Urine		Bone marrow	Hematologic response	
		κ	λ	κ/λ	SPEP	SIFE	UPEP	UIFE	%Plasma cells	IMWG	ISA
LCPT-1	Diagnosis	126	1.95	64.6	IgMκ	IgMκ	Negative	κ	3%, κ>λ	-	-
	Response	0.628	0.215	2.92	Negative	Negative	Negative	Negative	Normal	CR	CR
	preKTx	0.628	0.215	2.92	Negative	Negative	Negative	Negative	Normal	CR	CR
	postKTx	0.71	0.59	1.20	Negative	Negative	Negative	Negative	ND	-	-
	Final visit	0.93	1.24	0.75	Negative	Negative	Negative	Negative			
LCPT-2	Diagnosis	*a*	-	-	-	-	-	-	-	-	-
	preKTx	ND	ND	ND	Negative	Negative	Negative	κ	ND	Naive	Naive
	postKTx	N/A	N/A	N/A	Negative	Negative	Negative	IgAκ	ND		
	Recurrence	ND	ND	ND	Negative	Negative	Negative	IgAκ	10%, κ>λ		
	Response	6.40	2.01	3.18	Negative	Negative	Negative	IgAκ	1	VGPR	VGPR
	Final visit	9.91	2.03	4.88	Negative	Negative	Negative	IgAκ	1		
LCPT-3	Diagnosis	N/A	N/A	N/A	IgAκ	IgAκ	Negative	IgAκ	2%, κ>λ		
	preKTx	N/A	N/A	N/A	Negative	IgAκ	Negative	Negative	4%, κ>λ	Naive	Naive
	postKTx	N/A	N/A	N/A	Negative	IgAκ	Negative	Negative	ND		
	Recurrence	16.6	0.36	46.1	Negative	IgAκ	Negative	Negative	10–20%, κ>λ		
	Response	1.71	UD	UD	Negative	IgAκ	Negative	Negative	<1%	VGPR	VGPR
	Final visit	UD	UD	UD	Negative	IgAκ	Negative	Negative			
LCPT-4	Diagnosis	*a*	-	-	-	-	-	-	-		
	preKTx	N/A	N/A	N/A	κ	κ	κ	κ	7%, κ>λ	Naive	Naive
	postKTx	N/A	N/A	N/A	κ	κ	κ	κ			
	Recurrence	527	3.22	164	κ	κ	κ	κ	ND		
	Final visit	527	3.22	164	κ	κ	κ	κ			

[a]The diagnosis was made retrospectively after the kidney transplantation following histological examination of the native kidney biopsy. CR: complete response; IMWG: International Monoclonal Gammopathy Working Group; ISA: International Society of Amyloidosis; MM: multiple myeloma; N, Normal; N/A: not applicable (Some of the studies were not available due to the unavailability of free light chain assay at that time, or due to the retrospective diagnosis of MGRS after revision of native kidney biopsy); ND: Not done; PCD, plasma-cell dyscrasia; sFLC: serum free light chain; SIFE:

serum immunofixation electrophoresis; SPEP: serum protein electrophoresis; UD: undetectable; UIFE: urine immunofixation electrophoresis; UPEP: urine protein electrophoresis; VGPR: very good partial response.