# Kidney Transplantation in Monoclonal Immunoglobulin Deposition Disease: A Report of 6 Cases

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Monoclonal immunoglobulin deposition disease (MIDD) usually leads to kidney failure. Treatment of patients with a bortezomib-based regimen followed by autologous stem cell transplantation (SCT) has been increasingly used, with improvements in the response rates and allograft outcomes in kidney transplant recipients. The objective of this report was to analyze the outcomes of 6 patients who underwent kidney transplantation in our institution after treatment of MIDD between 2010 and 2019. Monoclonal immunoglobulin deposition disease was initially treated with bortezomib-based therapy followed by high-dose melphalan and autologous SCT with complete hematologic response, although all patients remained on dialysis. During a median follow-up of 20.5 months from kidney transplant (54 months from SCT), 1 patient experienced hematologic relapse and 2 had hematologic progression (one of them with MIDD relapse in the allograft) requiring treatment. The patient with organ relapse received daratumumab monotherapy, achieving complete hematologic response but with graft failure. The other 5 patients had functional grafts with median serum creatinine 1.68 mg/dL. These results support that, in patients with MIDD and sustained complete hematologic response, a kidney transplant can be considered. The optimal approach to treatment of hematologic relapse or recurrence of MIDD after kidney transplant remains to be determined.

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## Introduction

Monoclonal immunoglobulin deposition disease (MIDD) is a rare disease characterized by deposition of monoclonal light and/or heavy chains. Kidney involvement is the major manifestation in most patients and consists of hypertension, nephrotic syndrome, and/or decreased glomerular filtration rate that can evolve to kidney failure.[1]

The treatment of MIDD has been based on control of the underlying clonal plasma cell disorder. Conventional chemotherapy, used in patients with multiple myeloma (MM), has shown suboptimal results in this setting.[2] In recent years, treatment with a bortezomib-based regimen followed by high-dose intravenous melphalan and autologous stem cell transplantation (ASCT) has been increasingly used, with significant improvements in overall response rates[3-6] and kidney outcomes. In contrast with past recommendations,[7] if complete hematologic response is achieved, kidney transplantation (from deceased or living donor) has been considered in patients with kidney failure.[8,9]

The objective of this report is to describe our experience in recent years with patients who underwent kidney transplant after bortezomib and high-dose intravenous melphalan and ASCT[10] treatment of MIDD.

The treatment approach to MIDD-associated kidney disease in our institution is depicted in Fig 1. Complete remission (CR) was defined as normalization of serum free light chain (sFLC) ratio (to 0.82-3.6)[11] in the absence of a detectable monoclonal protein by serum and urine immunofixation electrophoresis. We applied this sFLC ratio range to patients with estimated glomerular filtration rate (eGFR) <55 mL/min based on its utility in studies. Very good partial response was defined as a decrease in the difference between involved and noninvolved sFLC to <40 mg/L. Kidney waiting list inclusion criteria were assessed by the treating hematologist and nephrologist according to local guidelines after at least 1 year in stable CR, given that lower tumor burden in patients with MIDD compared to MM impacts on longer response times after hematologic CR is obtained. Hematologic CR was confirmed by bone marrow aspiration with absence of minimal residual disease (MRD) assessed by flow cytometry before inclusion in the waiting list for kidney transplantation. At the time of the assessment of these patients before kidney transplant, the sensitivity for MRD by flow cytometry was generally 1 in 10,000, but flow cytometry sensitivity has improved significantly in more recent years.

Hematologic relapse was defined as reappearance of serum and/or urine M-protein by immunofixation and/or electrophoresis in a patient previously in CR. Hematologic progression was defined as absolute increase of involved FLC >100 mg/L.

Allograft dysfunction was defined as an unexplained and persistent ≥25% increase in serum creatinine level (Scr) from baseline (irrespective of the interval of time between baseline and the 25% increase; and in the absence of potential confounding factors), or new-onset proteinuria (defined as urinary albumin-creatinine ratio ≥0.2 mg/mg or a urinary protein-creatinine ratio >0.5 mg/mg).

According to our hospital protocol, urine protein excretion is measured once in the first month posttransplant, and every 2 to 3 months thereafter. Serum creatinine is assessed daily for 7 days or until hospital discharge, whichever occurs sooner; after discharge it is measured

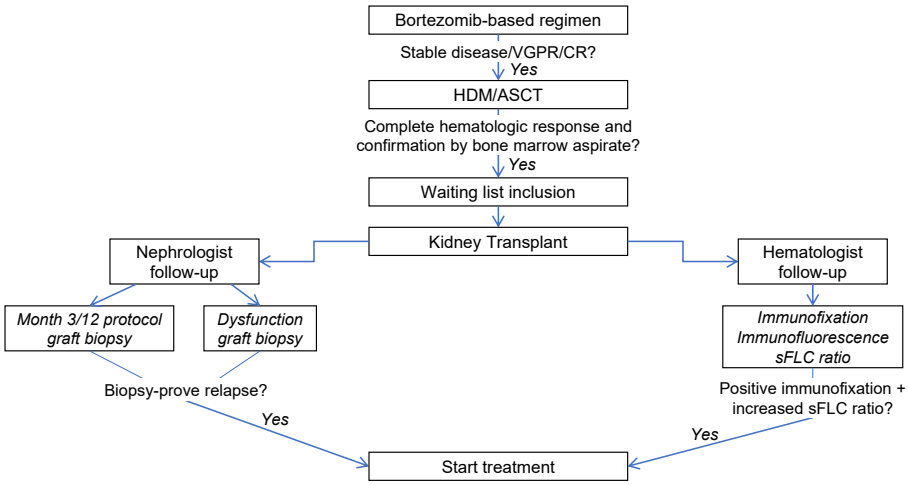


**Figure 1.** Protocol scheme.

weekly during the first month, every 2 weeks until the third month, monthly until the sixth month, and every 2 to 3 months thereafter. Hematologic recurrence without increased Scr or proteinuria was not an indication for kidney transplant biopsy.

## Case Reports

Six patients were diagnosed with MIDD by kidney biopsy between 2008 and 2017 and underwent a kidney transplant at our institution between June 2010 and July 2019 (Table 1). Five patients had light chain deposition disease and 1 had light and heavy chain deposition disease. Clinical presentation was kidney failure with proteinuria without nephrotic syndrome. Monoclonal gammopathy was detected in serum and/or urine of all patients (κ light chain in 5 patients). Three patients initiated maintenance hemodialysis during the diagnostic process, while it was started at 3, 5, and 44 months after diagnosis in the other 3 patients.

To assess extrarenal involvement, all patients included in the report underwent thorough clinical assessment including a full physical examination and extensive laboratory testing. Cardiac biomarker measurements (BNP [brain natriuretic peptide], NTproBNP [N-terminal fragment of the prohormone BNP], and/or troponins), as well as electrocardiogram, chest radiograph, skeletal survey, and echocardiogram, were performed systematically. When extrarenal organ involvement was suspected clinically, a specific imaging study and histological sampling were performed.

Initial chemotherapy consisted of bortezomib/dexamethasone in 5 patients and bortezomib/thalidomide/dexamethasone in 1 patient. After this bortezomib-based induction therapy, 4 patients (66%) achieved a hematologic response (either CR or very good partial response). Three months after SCT, all patients achieved hematologic CR but remained dialysis dependent. Patient 6 achieved a minimum sFLC ratio of 3.76 and was considered as having achieved CR based on criteria extrapolated from patients with MM.[1] Hematologic CR was confirmed by bone marrow aspiration with absence of MRD assessed by flow cytometry in 5 patients before inclusion in the waiting list for kidney transplantation. The patient without MRD assessment had negative results for immunofixation in serum and urine and no abnormal plasma cells were detected by morphology (<1%) in a bone marrow aspiration. No maintenance or consolidation treatment was given to any of the patients.

Median time from hematologic response to kidney transplant was 24 (range, 12-42) months. Immunosuppressive treatment is shown in Table 1. Patients 3 and 4 developed delayed graft function, though patient 3 (who had biopsy-proven acute tubular necrosis) did not recover function by the time of discharge. At discharge post-transplant, no patients displayed light chain recurrence on urinary immunofixation. During a median follow-up of 20.5 (range, 8-115) months after kidney transplant and 54 (range, 20-136) months after SCT, hematologic relapse occurred in 3 patients. Two of the relapsers developed hematologic progression, including 1 with recurrent MIDD in the transplant kidney and allograft failure 46 months after transplantation. The other 3 patients remain in hematologic CR with no organ progression at 6, 13, and 14 months after kidney transplantation (Fig S1). Median Scr at last follow-up in the patients with functional grafts was 1.68 (range, 1.2-1.82) mg/dL.

In patient 1, monoclonal κ light chain reappeared in urine by immunofixation 88 months after ASCT (66 months after kidney transplant). However, therapy was not started until 43 months after first positive immunofixation, when the serum-involved FLC value was 452 mg/dL and κ:λ light chain ratio increased up to 20. Second-line anti–plasma cell therapy with daratumumab was then administered, but no hematologic response was obtained.

**Table 1.** Baseline Characteristics and Evolution

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| Sex | F | F | M | M | M | M |
| Age, y | 59 | 52 | 45 | 56 | 49 | 60 |
| Date of dx (mo/y) | 3/2008 | 12/2015 | 09/2015 | 06/2011 | 12/2017 | 03/2013 |
| Scr at dx, mg/dL | 2.80 | 5.24 | 4.99 | 3.87 | 3.73 | 2.80 |
| Urine protein, mg/d | 6,329 | 290 | 12,460 | 6,682 | 500 | 7,000 |
| Chain type | κ | κ | κ | λ LC + HC | κ | κ |
| κ:λ ratio at dx | 2.30 | 11 | 5.21 | 0.27 | 27.8 | 260 |
| Plasma cells in BM | 16% | 20% | 5% | 13% | 9% | 10% |
| Non-kidney involvement | Cardiac | No | Cardiac | No | No | Cardiac + lung |
| Months to ASCT after dx | 5 | 10 | 12 | 7 | 7 | 13 |
| Months to KT after dx | 27 | 33 | 38 | 56 | 19 | 55 |
| IS scheme | ATG + MMF + FK + PDN | BLX + FK + EVE + PDN | ATG + FK + SRL + PDN | BLX + FK + EVE + PDN | ATG + EVE + FK + PDN | BLX + FK + MMF + PDN |
| Scr at discharge post KT, mg/dL | 1.09 | 1.82 | 6.84 (DGF) | 1.55 | 1.26 | 1.6 |
| Urine protein at discharge post KT, mg/dL | 174 | 178 | 3,128 (DGF) | 489 | 447 | 1,412 |
| Hematologic relapse | Yes (93 mo post-dx) | No | No | Yes (75 mo post-dx) | No | Yes (58 mo post-dx) |
| Hematologic progression | Yes (136 mo post-dx) | NA | NA | Yes (97 mo post-dx) | NA | No |
| Treatment of hematologic relapse | Daratumumab x3 | NA | NA | CyBorD + Daratumumab | NA | Watch and wait |
| Graft recurrence | N | N | N | Y (99 mo post-dx) | N | N |
| Scr at graft recurrence, mg/dL | NA | NA | NA | 2.5 | NA | NA |
| Allograft loss | N | NA | NA | Y (102 mo post-dx); return to HD | NA | N |
| Last f/u | 141 mo post-dx | 47 mo post-dx | 51 mo post-dx | 103 mo post-dx | 25 mo post-dx | 82 mo post-dx |
| Scr at last f/u, mg/dL | 1.82 | 1.68 | 1.2 | KRT | 1.3 | 1.7 |
| Urine protein at last f/u, mg/d | 139 | 50 | 69 | 3,615 | 58 | 2,131 |

Abbreviations: ASCT, autologous stem cell transplantation; ATG, thymoglobulin; BLX, basiliximab; BM, bone marrow; CyBorD, cyclophosphamide + bortezomib + dexamethasone; DGF, delayed graft function; dx, diagnosis; EVE, everolimus; F, female; f/u, follow-up; FK, tacrolimus; HC, heavy chain; HD, hemodialysis; IS, immunosuppressive; KRT, kidney replacemnt therapy; KT, kidney transplant; LC, light chain; NA, not applicable; M, male; MMF, mycophenolate; PDN, prednisone; Scr, serum creatinine; SRL, sirolimus.

After 4 cycles of therapy, daratumumab was discontinued and the patient has been followed under a "watch and wait" approach since. Treatment with a second ASCT was not considered because kidney biopsy did not show MIDD and proteinuria has remained below 200 mg/d. In patient 4, monoclonal λ light chain was detected in serum by immunofixation 67 months after ASCT and 19 months after kidney transplantation. Urine immunofixation also became positive 17 months after first positive serum immunofixation. Twenty-two months after hematologic relapse, cyclophosphamide, bortezomib, and dexamethasone was initiated because of an increase in proteinuria (2 g/d) and decreased GFR. The λ light chain values also had increased up to 584 mg/d. After 1 cycle of treatment without hematologic response, this regimen was changed to daratumumab monotherapy. With this approach, an early hematologic response was obtained (CR after 1 cycle) but without improvement of proteinuria or GFR. Daratumumab was stopped after 2.5 cycles because of erythroblastopenia and CR maintenance. Bone marrow biopsy was not performed to confirm CR. Kidney biopsy showed λ light chain deposition in the kidney graft and the patient initiated dialysis in January 2020. Finally, patient 6 had a hematologic relapse with reappearance of κ light chain in urine by immunofixation 45 months after ASCT (3 months after kidney transplant). Given that the serum κ FLC has remained within normal values, with a normal sFLC ratio, and there has been no increase in proteinuria or evidence of light chain deposition in the kidney biopsy, no rescue treatment has been initiated.

## Discussion

Few reports of patients with MIDD who undergo kidney transplantation have been published. In 2004, a Mayo Clinic team reported the outcomes of 7 patients with MIDD who underwent a kidney transplant during the period 1990-1998.[7] Treatment for the underlying malignant monoclonal gammopathy was only given in 3 patients and consisted of melphalan and prednisone administered pretransplant in 2 cases and posttransplant in 1. Graft recurrence developed in 5 patients after a mean of 33.3 months and the graft was lost after a mean of 11 months upon recurrence. Of the 2 remaining patients, 1 received chemotherapy after kidney transplant but died 3 months later and the other received pretransplant treatment and after 13 years remained alive and free of disease.

More recently, Sayed et al[8] reported the outcomes of 7 kidney transplant recipients treated at the UK National Amyloidosis Center. Three patients had graft loss during their follow-up, due to MIDD recurrence in 2 cases (at 1.6 and 1.9 years after transplantation) and graft rejection in 1. Patients with MIDD recurrence were those who did not receive anti–plasma cell therapy or ASCT before kidney transplant. The 4 remaining patients had GFRs over 40 mL/min at last follow-up.

In 2016, an updated report from the Mayo Clinic described their experience with kidney transplant in MIDD during the years 1992-2014.[9] Of the 9 kidney transplant recipients, 3 had graft recurrence. One of these patients, who had not received anti–plasma cell therapy, had MIDD recur at 33 months after kidney transplant. The second received chemotherapy but had no hematologic response and relapsed 7 years later, and the last patient received proteasome inhibitor–based therapy with CR and had recurrence in the allograft 9 years after treatment.

Similar to the Mayo Clinic cases, our experience shows that good results are obtained if patients achieved complete response with a bortezomib-based regimen plus ASCT before kidney transplantation. However, the risk of recurrence still exists, and close follow-up should be performed. In the previously described series, all the patients with kidney relapse lost their graft, but no data are available about those patients who experienced hematologic relapse without evidence of graft relapse. In this context early detection and re-treatment might prevent graft loss. Also, protocol biopsies may be useful for early histological relapse identification and comparison with subsequent biopsies for analysis of treatment response and accumulated chronic damage. It is also important to identify risk factors for MIDD relapse. In this sense MRD assessment before kidney transplant should be considered. Two of the relapsed patients in our cohort underwent kidney transplantation after confirmation of absence of MRD; for the third one, no MRD testing was available. Achieving sustained hematologic CR, with negative immunofixation and normalization of the sFLC ratio, is imperative to considering kidney transplantation. Additionally, kidney transplantation should be considered in patients with CR, even if they do have detectable MRD, given the evidence of improved progression-free and overall survival.

Although none of our cohort received living donor kidney transplants, we do not consider these transplants to be contraindicated in patients with MIDD given the absence of a reported increased risk of recurrence in this setting by others.[7] However, the limited number of cases and lack of information make this difficult to assess. In other hematologic pathologies like amyloid light-chain (AL) amyloidosis, living donor kidney transplant has been described as a good option.[12]

According to our institution's protocol, close monitoring of monoclonal gammopathy and kidney function is performed after kidney transplantation. Once hematologic relapse is detected, the decision on the best time to start anti–plasma cell therapy should be carefully considered, depending on several factors such as patient age, previous therapy and time to relapse, prior toxicities and response, dynamics of sFLC increase, presence of proteinuria, and kidney function or findings on graft biopsy, if available. In our experience, a watch and wait approach with close follow-up might be an option in selected patients with isolated hematologic relapse. When hematologic or histological progression are detected, anti–plasma cell therapy should be started (cyclophosphamide, bortezomib, and dexamethasone; or daratumumab), and the possibility of a second ASCT considered if previous hematologic response was of long-term duration.

One limitation of our findings is that the median posttransplant follow-up in our patients could be considered short for graft recurrence of MIDD (<2 years in half of the cohort); however, it is a reasonable time frame to detect hematologic relapse and progression based on prior reports.[8,9] Follow-up time of the 3 patients who did not have hematologic relapse in our cohort were less than 4 and 2 years from ASCT and kidney transplant, respectively. In the previous series described, graft relapse occurred after second year of kidney transplant in 6 out of the 10 reported relapse cases, indicating graft relapse is likely. As in AL amyloidosis, the lower tumor burden of patients with MIDD compared to MM impacts on longer response times after hematologic CR is obtained. On the basis of our experience and that reported in the literature, we have decided to set a threshold of at least 1 year of CR after ASCT before considering kidney transplant.

In conclusion, kidney transplantation should be considered in patients with MIDD and kidney failure who have achieved stable hematologic CR after anti–plasma cell therapy, preferably including a bortezomib-based regime and ASCT. Closely coordinated follow-up should be done posttransplant to detect early hematologic and kidney recurrence. The optimal approach to treatment of hematologic relapse or recurrence of MIDD after kidney transplant remains to be determined.

## Supplementary Material

**Supplementary File (PDF)**

**Figure S1**: Patients' hematologic and kidney outcomes following HDM/ASCT.

## Article information

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