Renal Monoclonal Immunoglobulin Deposition Disease: A Report of 64 Patients from a Single Institution

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Summary

Background and objectives To better define the clinical-pathologic spectrum and prognosis of monoclonal immunoglobulin deposition disease (MIDD), this study reports the largest series.

Design, setting, participants, & measurements Characteristics of 64 MIDD patients who were seen at Mayo Clinic are provided.

Results Of 64 patients with MIDD, 51 had light chain deposition disease, 7 had heavy chain deposition disease, and 6 had light and heavy chain deposition disease. The mean age at diagnosis was 56 years, and 23 patients (36%) were ≤50 years of age. Clinical evidence of dysproteinemia was present in 62 patients (97%), including multiple myeloma in 38 (59%). M-spike was detected on serum protein electrophoresis in 47 (73%). Serum free light chain ratio was abnormal in all 51 patients tested. Presentation included renal insufficiency, proteinuria, hematuria, and hypertension. Nodular mesangial sclerosis was seen in 39 patients (61%). During a median of 25 months of follow-up (range, 1–140) in 56 patients, 32 (57%) had stable/improved renal function, 2 (4%) had worsening renal function, and 22 (39%) progressed to ESRD. The mean renal and patient survivals were 64 and 90 months, respectively. The disease recurred in three of four patients who received a kidney transplant.

Conclusions Patients with MIDD generally present at a younger age than those with light chain amyloidosis or light chain cast nephropathy. Serum free light chain ratio is abnormal in all MIDD patients, whereas only three-quarters have abnormal serum protein electrophoresis. The prognosis for MIDD is improving compared with historical controls, likely reflecting earlier detection and improved therapies.


Introduction

Monoclonal immunoglobulin deposition disease (MIDD) is a rare disease characterized by the deposition of monoclonal Ig molecules in basement membranes. In contrast to amyloidosis, the deposits in MIDD are nonfibrillar and Congo-red negative. MIDD includes three subtypes depending on the composition of deposits: light chain deposition disease (LCDD), the most common subtype, in which the deposits are composed of monoclonal light chains only; light and heavy chain deposition disease (LHCDD), in which the deposits are composed of monoclonal light and heavy chains; and heavy chain deposition disease (HCDD), in which the deposits are composed of monoclonal heavy chains only. The monoclonal light chains in LCDD are mainly of the κ isotype (92%), and the majority belong to the V_κIV subgroup (1,2). The deposits in HCDD are composed of the γ heavy chain, which typically lacks the first constant domain (CH1) (1,3,4). Renal involvement is almost always present in MIDD. Patients typically present with renal insufficiency and proteinuria, often accompanied by nephrotic syndrome. The characteristic morphologic features of renal MIDD include the following: nodular sclerosing glomerulopathy by light microscopy; diffuse linear staining of glomerular basement membranes (GBMs) and tubular basement membranes (TBMs) for a single light chain (LCDD), a single light chain and a single heavy chain (LHCDD), or a single heavy chain without light chains (HCDD) by immunofluorescence; and nonfibrillar, “powdery” electron-dense deposits in GBMs and TBMs detected by electron microscopy (1).

Analysis of the literature on renal MIDD is confounded by the misuse in some studies of the designation “MIDD” as a generic term for a variety of diseases induced by tissue deposition of Ig, including amyloid, Randall-type MIDD, myeloma cast nephropathy (MCN), and proliferative GN with monoclonal IgG deposits (5,6), as well as the lack of ultrastructural confirmation of MIDD in some reported patients (7). Furthermore, in some studies, patients with pure MIDD and those with coexistent MCN were aggregated (7,8). Combined MIDD and MCN, reported in 16%–46% of patients with MIDD (1,7,8), has clinical features and outcomes that more closely resemble those in MCN than pure MIDD (1). We report our experience with 64 patients with MIDD who were seen at...
the Mayo Clinic in Rochester, Minnesota, and were followed for a median of 25 months (range, 1–140). The large cohort of patients in this study has the advantage of allowing us to better define the disease’s demographics, hematologic and renal characteristics, histologic findings, prognostic indicators, and outcomes.

Materials and Methods

Seventy-three Mayo Clinic patients with a diagnosis of renal MIDD were identified by retrospective review of all native renal biopsies evaluated in the Renal Pathology Laboratory at the Mayo Clinic from 1992 to 2011. During the study period, the total number of native kidney biopsies from Mayo Clinic patients was 10,481. This indicates that the biopsy incidence of MIDD in our medical center is 0.7%. Nine patients were excluded from this study because of the lack of renal tissue for immunofluorescence in two patients, presence of concurrent MCN in five patients, and presence of concurrent extensive renal amylod in two patients. The remaining 64 patients that were included in this study fulfilled the following two diagnostic criteria of MIDD: (1) the presence of diffuse linear monoclonal protein deposition along GBMs and TBMs on immunofluorescence (i.e., staining exclusively for \( \kappa \) or for \( \lambda \) in the case of LCDD, staining for a single class of Ig \([\gamma, \alpha, \text{or } \mu]\) with light-chain restriction in the case of LHCD, or staining for a single class of Ig \([\gamma, \alpha, \text{or } \mu]\) with no corresponding light chain in the case of HCDD); and (2) the presence of corresponding punctate, “powdery” electron-dense deposits along GBMs or TBMs on electron microscopy.

Standard processing of renal biopsies included light microscopy, immunofluorescence, and electron microscopy. For light microscopy, hematoxylin and eosin, periodic acid–Schiff, Masson’s trichrome, and Jones methamine silver staining were used. Standard immunofluorescence on frozen tissue was performed in 63 biopsies with available glomeruli. In the remaining biopsy, no tissue was submitted for immunofluorescence and therefore immunofluorescence was performed on pronase-digested paraffin-embedded tissue (9). For immunofluorescence, 3-μm cryostat sections were stained with polyclonal FITC-conjugated antibodies to IgG, IgM, IgA, C3, C1q, \( \kappa \), and \( \lambda \) (Dako Corp, Carpinteria, CA). Determination of the IgG subclass was performed on 3-μm cryostat sections using monoclonal FITC-conjugated antibodies to IgG1, IgG2, IgG3, and IgG4 (Sigma-Aldrich Corp, St. Louis, MO).

Demographic information, presenting renal clinical and laboratory findings, and hematologic clinical and laboratory findings (including bone marrow biopsy findings), treatment and follow-up, were obtained from patients’ electronic medical records. The following clinical definitions were used: nephrotic-range proteinuria (NRP); \( \geq 3.0 \text{ g/day} \); hypoalbuminemia: serum albumin <3.5 g/dl; renal insufficiency: serum creatinine >1.2 mg/dl; nephrotic syndrome: NRP with hypoalbuminemia and peripheral edema; hypertension: systolic BP >140 mmHg, diastolic BP >90 mmHg, or ongoing treatment with antihypertensive medications; hypercalcemia: calcium >10.1 mg/dl; abnormal free light chain (FLC) ratio: serum free \( \kappa/\lambda \) ratio <0.26 or >1.65; markedly abnormal FLC ratio: serum free \( \kappa/\lambda \) ratio <0.125 or >8; and multiple myeloma (MM): renal MIDD plus \( \geq 10\% \) monoclonal plasma cells in the bone marrow and monoclonal protein identified in the serum and/or urine (10). Tubular atrophy and interstitial fibrosis (TA/IF) were graded on a semiquantitative scale based on an estimate of the percentage of renal cortex affected and recorded as follows: 0, none; 1%–25%, mild; 26%–50%, moderate; or >50%, severe.

Continuous variables are reported as the mean ± SD. Statistical analysis was performed using SPSS for Windows software (version 17; SPSS, Chicago, IL) and StatXact software (version 9; Cytel Corporation, Cambridge, MA). Analysis was performed using nonparametric exact statistical methods. Univariate analysis was performed using the Mann–Whitney–Wilcoxon test, the Kruskal–Wallis test, and the Fisher–Freeman–Halton exact test, as appropriate for variable type. Survival analysis for progression to ESRD was performed by the Kaplan–Meier method using the log-rank test for univariate analysis and the Cox proportional hazards model for multivariate analysis. Statistical significance was assumed at \( P<0.05 \).

This study was approved by the Institutional Review Board of the Mayo Clinic Foundation.

Results

Pathologic Findings

Table 1 details the pathologic findings. Nodular mesangial sclerosis was present in 39 patients (61%) (Figure 1). The mesangial nodules were generally positive for periodic acid–Schiff, trichrome blue, and silver-positive. Five additional patients (8%) showed mild mesangial sclerosis without nodule formation. The remaining patients did not show mesangial sclerosis (Figure 2). There was no significant thickening of the GBMs, except in two patients who had overlapping features of diabetic nephropathy. Variable degrees of membranoproliferative features with GBM duplication and mesangial hypercellularity and interposition were noted in some patients. Six patients (9%) (including four with LCDD, one with LHCD, one with HCDD) showed focal cellular crescents. The degrees of TA/IF and arteriosclerosis were variable (Table 1). Two patients (3%) showed focal direct interstitial infiltration by neoplastic plasma cells (Figure 3).

On immunofluorescence, all 64 patients by definition showed diffuse linear monoclonal deposits along GBMs and TBMs (Figure 4). Most patients also had arterial wall deposits. The dominant monoclonal proteins detected by immunofluorescence are listed in Table 1. Tissue was available for IgG subtype staining by immunofluorescence in two of the four patients with IgG \( \kappa \) LHCD and four of the six patients with \( \gamma \) HCDD. The IgG subtype in the two patients with IgG \( \kappa \) LHCD was IgG1 in one and IgG4 in one. The IgG subtype in the four patients with \( \gamma \) HCDD was IgG4 in two, IgG1 in one, and IgG2 in one. Granular to linear glomerular deposition of C3 was detected in three patients with LHCD and three patients with HCDD, whereas weak glomerular deposition of C1q was detected in one patient with LHCD and two patients with HCDD.

On electron microscopy, by definition, all patients showed punctate “powdery” electron-dense deposits along the outer aspect of the TBMs and/or the inner aspect of the lamina densa of GBMs (Figure 5). The deposits were seen along TBMs in 100% of patients (58 of 58 patients in
which they were looked for), along the lamina densa of GBMs in 95% of patients (58 of 61 patients with available glomeruli for electron microscopy), and in the expanded mesangium in 72% patients (44 of 61 patients with available glomeruli for electron microscopy). Mesangial deposits tended to be more common in HCDD than LCDD (P=0.09).

**Clinical Characteristics**

Table 2 details the demographics and clinical renal characteristics at biopsy. The male/female ratio of the 64 patients was 1.9:1. The mean age was 56 years (range, 22-83). Five percent of patients were 22-30 years of age, 6% were 31-40 years of age, 25% were 41-50 years of age, and 64% were >50 years of age. A 24-hour urine protein quantitation, performed in 59 patients, was abnormal (>150 mg) in all but two patients (97%). The mean 24-hour urine protein was 4.1 g, which was higher in HCDD than LCDD (P=0.001) and LHCDD (P=0.06). NRP and nephrotic syndrome were more frequent in HCDD than LCDD (P=0.004 and P=0.02, respectively). Peripheral edema was more common in HCDD than LCDD (P=0.02). Microhematuria was documented in 62% of patients, whereas gross hematuria was present in only 3% of patients.

Table 3 details the hematologic characteristics at biopsy. Overall, 97% of patients had clinical evidence of dysproteinemia, which was κ-type in 81% and λ-type in 19%. Dysproteinemia was detected 3-84 months before MIDD diagnosis in 19% of patients, within 1 month of MIDD diagnosis in 72%, and 4-36 months after MIDD diagnosis in the remaining 8%. M-spike was detected on serum protein electrophoresis (SPEP)/serum immunofixation electrophoresis (SIFE) or urine protein electrophoresis (UPEP)/urine immunofixation electrophoresis (UIFE) in 86% of patients. LHCDD patients were more likely to have a monoclonal whole Ig on UPEP/UIFE than LCDD patients (P=0.01) and HCDD patients (P=0.08). Serum FLC assay was performed in 51 patients (80%) who were seen at the Mayo Clinic after 2002. Serum FLC ratio was abnormal in all of these patients (100%), and was markedly abnormal in 78% of them. Thirty-eight MIDD patients (59%) fulfilled the established diagnostic criteria for MM (10), which was diagnosed before or at the time of kidney biopsy in all but one patient. One patient with κ-LCDD had lymphoplasmacytic lymphoma. Only two patients had biopsy-proven heart involvement. Three additional patients had an abnormal echocardiogram (suggestive of an infiltrative process) but no biopsies were performed. None of the patients had biopsy-proven involvement of the liver or any other organ. None of the 19 patients who died had autopsies done at the Mayo Clinic; therefore, the extent of asymptomatic extrarenal involvement in these patients could not be determined.

**Treatment and Outcomes**

No renal follow-up data were available for four patients, and four patients died within 1 month after kidney biopsy. The remaining 56 patients (88%) were followed for a mean of 34 months (median 25; range, 1-140). Eight patients

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**Table 1. Pathologic findings**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCDD</th>
<th>HCDD</th>
<th>LHCDD</th>
<th>All MIDD Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>51</td>
<td>7</td>
<td>6</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Mean number of glomeruli</td>
<td>18 (2-150)</td>
<td>15 (9-25)</td>
<td>12 (3-25)</td>
<td>17 (2-150)</td>
<td>0.64</td>
</tr>
<tr>
<td>Mean % of globally sclerotic glomeruli</td>
<td>24 (0-95)</td>
<td>15 (0-50)</td>
<td>21 (0-63)</td>
<td>23 (0-95)</td>
<td>0.73</td>
</tr>
<tr>
<td>Nodular mesangial sclerosis</td>
<td>30 (59)</td>
<td>6 (86)</td>
<td>3 (50)</td>
<td>39 (61)</td>
<td>0.34</td>
</tr>
<tr>
<td>Degree of tubular atrophy and interstitial fibrosis</td>
<td>none</td>
<td>mild</td>
<td>moderate</td>
<td>marked</td>
<td></td>
</tr>
<tr>
<td>Degree of arteriosclerosis</td>
<td>none</td>
<td>mild</td>
<td>moderate</td>
<td>marked</td>
<td></td>
</tr>
<tr>
<td>Monoclonal protein components detected by immunofluorescence</td>
<td>43 κ (84); 8 λ (16)</td>
<td>6 γ (86); 1 α (14)</td>
<td>4 γ and κ (67); 1 α and λ (17)</td>
<td>43 κ (67); 8 λ (13); 6 γ (9); 4 γ and κ (6); 1 α (2); 1 α and κ (2); 1 α and λ (2)</td>
<td></td>
</tr>
<tr>
<td>Mesangial deposits on electron microscopy</td>
<td>31/48 (65)</td>
<td>7 (100)</td>
<td>6 (100)</td>
<td>44/61 (72)</td>
<td>0.04*</td>
</tr>
<tr>
<td>GBM deposits on electron microscopy</td>
<td>46/48 (96)</td>
<td>6 (86)</td>
<td>6 (100)</td>
<td>58/61 (95)</td>
<td>0.52</td>
</tr>
<tr>
<td>TBM deposits on electron microscopy</td>
<td>46/46 (100)</td>
<td>7 (100)</td>
<td>5/5 (100)</td>
<td>58/58 (100)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data are presented as mean (range) or n (%) unless otherwise specified. LCDD, light chain deposition disease; HCDD, heavy chain deposition disease; LHCDD, light and heavy chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; GBM, glomerular basement membrane; TBM, tubular basement membrane.

*Post hoc subset analysis: LCDD versus HCDD, P=0.09; LCDD versus LHCDD, P=0.16; HCDD versus LHCDD, P=1.00.
(14%) were not treated with chemotherapy, five of whom (63%) progressed to ESRD. Thirty-two patients (57%) were treated with chemotherapy, 11 of whom (34%) progressed to ESRD. Chemotherapy consisted of dexamethasone alone in two patients; melphalan and dexamethasone in six; melphalan, cyclophosphamide, and dexamethasone in two; melphalan, bortezomib, and dexamethasone in three; melphalan, thalidomide, and dexamethasone in one; cyclophosphamide and dexamethasone in two; azathioprine and dexamethasone in one; lenalidomide and dexamethasone in three; and rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone in one with lymphoma. The remaining 16 patients (29%) were treated with autologous stem cell transplant (SCT), 6 of whom (38%) progressed to ESRD (Table 4).

On follow-up in these 56 patients, 32 patients (57%) had stable/improved renal function, 2 (4%) had worsening renal function (>50% increase in serum creatinine from creatinine at biopsy but not reaching ESRD), and 22 (39%) progressed to ESRD. The mean renal survival was 64.0 months, which was not statistically different for LCDD, LHCDD, and HCDD ($P=0.79$)(Table 4).

Four of the 22 patients who progressed to ESRD (3 with LCDD and 1 with LHCDD) received a kidney transplant. Three of these four patients (75%) had biopsy-proven disease recurrence diagnosed 43, 11, and 7 months after transplant. The recurrent disease in one patient was treated with dexamethasone and melphalan for 9 months, followed by lenalidomide for 3 months (stopped due to side effects) then bortezomib for 5 months. Chemotherapy led to a significant reduction in serum free $\kappa$. At last follow-up 73 months after transplant, allograft function was slightly decreased (serum creatinine 1.5 mg/dl). The second patient with recurrent disease was treated with prednisone for concurrent rejection. At the time of death (of unknown cause) 37 months after transplant, serum creatinine was elevated at 2.3 mg/dl. The third patient with recurrent disease who also had direct myeloma infiltration of the renal allograft was treated with bortezomib and dexamethasone. Treatment was ineffective; he lost his allograft and died of refractory MM 8 months after transplant.

Using Cox regression, predictors of reaching ESRD on univariate analysis were higher serum creatinine at biopsy ($P<0.001$) and low hemoglobin at biopsy ($P=0.01$). Higher proteinuria at biopsy ($P=0.07$) and absence of treatment with SCT ($P=0.08$) were marginally significant. Using the Cox proportional hazards model, the only independent predictor of the rate of progression to ESRD on multivariate analysis was serum creatinine at biopsy ($P=0.003$) (hazard ratio, 1.477; 95% confidence interval, 1.140–1.914). Type of therapy and pathologic parameters (percentage of global glomerulosclerosis, degree of TA/IF and arteriosclerosis) did not predict renal survival.

Follow-up 24-hour urine protein quantitation was performed in 30 of the 34 patients who did not progress to ESRD. Of these 30 patients, 6 (20%) had disappearance of the proteinuria, 15 (50%) had a >50% reduction in proteinuria, 7 (23%) had stable proteinuria, and only 2 (7%) had >50% increase in proteinuria. The mean final 24-hour urine protein in these 30 patients was 1.2 g.

Of the 60 patients with available patient survival data, 19 (32%) died. The mean patient survival was 90 months, which was not statistically different for LCDD, LHCDD, and HCDD ($P=0.42$). The mean time from biopsy to death in those who died was 18 months. By Cox regression, predictors of patient death on univariate analysis were older age ($P=0.01$), higher serum creatinine at biopsy.

 Figure 1. | Nodular sclerosing glomerulopathy. The glomerulus exhibits global nodular mesangial sclerosis with mild mesangial hypercellularity. The nodules are periodic acid–Schiff (PAS) positive. There is also thickening of tubular basement membranes by similar PAS positive material. Magnification, $\times200$.

 Figure 2. | MIDD without nodular mesangial sclerosis. No mesangial sclerosis was seen in 31% of patients in this study. This figure exhibits tubular simplification, luminal ectasia, interstitial fibrosis, and tubular basement membrane thickening by periodic acid–Schiff positive material. Glomeruli appear unremarkable without mesangial sclerosis. Magnification, $\times100$. 
(\(P=0.004\)), dialysis at biopsy \((P=0.007)\), low hemoglobin at biopsy \((P=0.05)\), presence of lytic bone lesions \((P=0.003)\), presence of MM \((P=0.009)\), presence of hypertension \((P=0.02)\), no treatment (versus chemotherapy alone or SCT) \((P=0.001)\), and no treatment or chemotherapy alone (versus SCT) \((P=0.001)\). Using the Cox proportional hazards model, the only independent predictor of death on multivariate analysis was the presence of lytic bone lesions \((P=0.04\); hazard ratio, 3.986; 95% confidence interval, 1.060–14.987).

**Discussion**

This study reports our experience with a series of 64 patients with MIDD, which is, to our knowledge, the largest clinical-pathologic series of MIDD. The mean age was 56 years; 36% of patients were ≤50 years of age and only 22% were elderly (>64 years of age). In comparison, the reported mean age at diagnosis was 66 years for MCN (11) and 62 years for light chain amyloidosis (12). Therefore, in patients with dysproteinemia, the chance of finding pure MIDD and not amyloid or MCN is higher in middle-aged adults compared with the elderly population. Patients with concurrent MIDD and MCN are older than those with pure MIDD (mean age, 67 versus 57 years in one study) (1). The male sex preponderance in our patient population is in agreement with prior studies (1,7,13).
In prior studies conducted before the availability of serum FLC assay, 13%–33% of patients with MIDD had no identifiable M-spike on SPEP or UPEP (1,14). Similarly, 14% of our study patients had negative SPEP/SIFE and UPEP/UIFE. Noticeably, among the seven patients with HCDD in our series, monoclonal whole Ig was detected by SPEP/SIFE in only four and by UPEP/UIFE in only one. In contrast, SPEP/SIFE detected IgG1 in all four HCDD patients reported by Moulin et al. (3). In most reported cases of yHCDD, there was a deletion of the CH1 domain in the...
circulated or deposited γ heavy chains (1,3,15), which is required for secretion of free heavy chains by plasma cells. The inability to detect a corresponding monoclonal heavy chain component in the serum in three of our patients may relate to its presence at very low titers, below the level of detection by our standard SIFE, or to rapid rates of tissue deposition (13). In addition, because many of the secreted heavy chains are truncated proteins, they may elude detection by standard SPEP/SIFE techniques. Importantly, in our study FLC ratio was abnormal in all 51 patients (100%) tested, including all 4 LHCDD and 4 HCDD patients found that the sensitivity of the abnormal FLC ratio was only 76% (16) and Kastritis et al. (17). The above data indicate that the sensitivity of the abnormal FLC ratio was also abnormal in all 10 MIDD patients re-tested, and was markedly abnormal in 87% of them. Serum monoclonal whole immunoglobulin none versus IgG/IgA 0.09a
IgG 13 (25) 1 (14) 3 (50) 38 (59) 0.17
IgA 6 (12) 2 (29) 3 (50) 38 (59) 0.17

Urine monoclonal whole immunoglobulin none versus IgG/IgA 0.03b
IgG 40/9 (82/18) 5/2 (71/29) 4/1 (63/31) 50/12 (81/19) 0.84

Data are presented as n (%) unless otherwise specified. LCDD, light chain deposition disease; HCDD, heavy chain deposition disease; LHCDD, light and heavy chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; SPEP/SIFE, serum protein electrophoresis/serum immunofixation electrophoresis; UPEP/UIFE, urine protein electrophoresis/urine immunofixation electrophoresis; FLC, free light chain.

Post hoc subset analysis: LCDD versus HCDD, P=0.42; LCDD versus LHCDD, P=0.07; HCDD versus LHCDD, P=0.56.
Post hoc subset analysis: LCDD versus HCDD, P=0.75; LCDD versus LHCDD, P=0.01; HCDD versus LHCDD, P=0.07.
Post hoc subset analysis: LCDD versus HCDD, P=1.00; LCDD versus LHCDD, P=0.01; HCDD versus LHCDD, P=0.08.

In this study, we found that some differences in clinicopathological features of HCDD compared with LCDD. NRP, peripheral edema, and nephrotic syndrome were more common in HCDD. There was also a tendency for more frequent mesangial deposits in HCDD. These differences may relate to the ability of the heavy chain to activate complement, a property that light chains lack. Complement activation, which is typically detectable by immunofluorescence in these cases, may have direct effects on mesangial cells and podocytes to promote matrix production and greater proteinuria (19,20). Patient outcome, however, was not statistically different between HCDD and LCDD. The clinical and pathologic features of LHCDD were generally not statistically different from LCDD.
the better patient outcomes in our series compared with prior studies (as shown in Table 5) suggests that the prognosis of MIDD has improved over the past decade, likely as a result of earlier diagnosis and the introduction of newer chemotherapeutic regimens including SCT. 

There are two noteworthy limitations of our study. First, the small sample size for HCDD and LHCDD likely limits the potential of finding differences among the groups and may produce random statistical effects. Therefore, our findings on statistical analysis should be interpreted with caution and further studies that include larger numbers of patients with LHCDD and HCDD are needed to confirm these findings. Second, the uncontrolled retrospective design, the lack of standardized therapy, and the relatively short follow-up may have contributed to the lack of statistical benefit of therapy in MIDD in our study. Prospective, multicenter, controlled studies of patients with MIDD are needed to determine the optimal therapeutic regimen, including the role of SCT.

In summary, MIDD is a rare dysproteinemia-related renal disease. LCDD comprises 80% of the cases, whereas LHCDD and HCDD comprise the remaining 20%. Contrary to light chain amyloidosis and MCN, pure MIDD is more common in middle-aged than elderly adults and may occur

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### Table 4. Treatment and outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCDD</th>
<th>HCDD</th>
<th>LHCDD</th>
<th>All MIDD Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>45</td>
<td>7</td>
<td>4</td>
<td>56</td>
<td>0.65</td>
</tr>
<tr>
<td>Mean/median duration of follow-up, mo (range)</td>
<td>35/26 (2–140)</td>
<td>20/12 (5–53)</td>
<td>53/58 (1–97)</td>
<td>34/25 (1–140)</td>
<td>0.65</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.55</td>
</tr>
<tr>
<td>none</td>
<td>6 (13)</td>
<td>2 (29)</td>
<td>0 (0)</td>
<td>8 (14)</td>
<td></td>
</tr>
<tr>
<td>chemotherapy without SCT</td>
<td>25 (56)</td>
<td>4 (57)</td>
<td>3 (75)</td>
<td>32 (57)</td>
<td></td>
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<tr>
<td>SCT</td>
<td>14 (31)</td>
<td>1 (14)</td>
<td>1 (25)</td>
<td>16 (29)</td>
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<td>Renal outcome, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.98</td>
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<tr>
<td>stable/improved</td>
<td>26 (58)</td>
<td>4 (57)</td>
<td>2 (50)</td>
<td>32 (57)</td>
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<tr>
<td>worsening renal functiona</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>progression to ESRD</td>
<td>17 (38)</td>
<td>3 (43)</td>
<td>2 (50)</td>
<td>22 (39)</td>
<td></td>
</tr>
<tr>
<td>mean time to ESRD (mo)</td>
<td>6</td>
<td>12</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Patient deaths, n (%)</td>
<td>15/48 (31)</td>
<td>1/7 (14)</td>
<td>3/5 (60)</td>
<td>19/60 (32)</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean time to death (mo)</td>
<td>20</td>
<td>12</td>
<td>7</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Renal survival, mo (mean ± SEM)</td>
<td>67.7 ± 8.7</td>
<td>26.4 ± 7.7</td>
<td>36.0 ± 24.9</td>
<td>64.0 ± 8.1</td>
<td>0.79</td>
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<tr>
<td>Patient survival, mo (mean ± SEM)</td>
<td>91.1 ± 10.7</td>
<td>42.8 ± 10.7</td>
<td>42.0 ± 20.0</td>
<td>90.4 ± 9.5</td>
<td>0.42</td>
</tr>
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</table>

LCDD, light chain deposition disease; HCDD, heavy chain deposition disease; LHCDD, light and heavy chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; SCT, stem cell transplant.

*Defined as >50% increase in final serum creatinine from creatinine at kidney biopsy.

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### Table 5. Outcome and prognostic indicators in MIDD in this study and in previous reports

<table>
<thead>
<tr>
<th>Study period</th>
<th>Pozzi et al. (7)a</th>
<th>Lin et al. (1)</th>
<th>This Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>63</td>
<td>23</td>
<td>64</td>
</tr>
<tr>
<td>MIDD subtype (n)</td>
<td>62 LCDD, 1 LHCDD</td>
<td>12 LCDD, 6 HCDD, 5 LHCDD</td>
<td>51 LCDD, 7 HCDD, 6 LHCDD</td>
</tr>
<tr>
<td>Duration of follow-up (mo)</td>
<td>Median 28</td>
<td>Mean 22</td>
<td>Mean 34 (median 25)</td>
</tr>
<tr>
<td>Patients who reached ESRD on follow-up (%)</td>
<td>57</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>Patients who died on follow-up (%)</td>
<td>59</td>
<td>43</td>
<td>32</td>
</tr>
<tr>
<td>Predictors of renal survival on multivariate analysis</td>
<td>Lower initial serum creatinine</td>
<td>Lower initial serum creatinine</td>
<td>Lower initial serum creatinine</td>
</tr>
<tr>
<td>Younger age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predictors of patient survival on multivariate analysis</td>
<td>Younger age</td>
<td>Absence of MM</td>
<td>Absence of lytic bone lesions</td>
</tr>
<tr>
<td>Absence of extrarenal involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MIDD, monoclonal immunoglobulin deposition disease; LCDD, light chain deposition disease; LHCDD, light and heavy chain deposition disease; HCDD, heavy chain deposition disease.

*aElectron microscopy was performed in only 70% of patients (in which “powdery” electron-dense deposits were seen in 77%). Sixteen percent of patients had concurrent myeloma cast nephropathy, which likely contributed to the poorer prognosis in this study.*
as early as the third decade of life. Patients typically present with renal failure, proteinuria, hematuria, and hypertension. NRFP and nephrotic syndrome are more common in HCDDD than LCDDD, possibly reflecting the effects of associated complement mediated injury. Serum FLC ratio is abnormal in most (if not all) patients and is more sensitive than standard SIFE and UIFE to detect the associated dysproteinemia. Histologically, the characteristic nodular sclerosing glomerulopathy is present in only two-thirds of patients, underscoring the importance of careful analysis by immunofluorescence. The prognosis in MIDD patients is improving compared with outcome data from historical case series. In this study, the mean renal and patient survivals were 64 and 90 months, respectively. Because 88% of our patients were diagnosed after 2000, it is likely that earlier detection and greater availability of modern therapeutic regimens, including SCT, have contributed to these improved outcomes. Patients with higher serum creatinine at biopsy have poorer renal survivals, emphasizing the paramount importance of early detection.

**Disclosures**

None.

**References**


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