Renal Monoclonal Immunoglobulin Deposition Disease: The Disease Spectrum

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Abstract. This study reports the clinicopathologic findings and outcome in 34 patients with renal monoclonal immunoglobulin deposition disease (MIDD), which included 23 light-chain DD (LCDD), 5 light- and heavy-chain DD (LHCDD), and 6 heavy-chain DD (HCDD). A total of 23 patients had pure MIDD, whereas 11 patients had LCDD with coexistent myeloma cast nephropathy (LCDD & MCN). Renal biopsy diagnosis preceded clinical evidence of dysproteinemia in 68% of all cases. By immunofluorescence, the composition of deposits included 11κ/1λ (LCDD), 3IgGκ/2IgGλ (LHCDD), 5γ/1α (HCDD), and 10κ/1λ (LCDD & MCN). Patients with pure MIDD presented with mean serum creatinine of 4.2 mg/dl, nephrotic proteinuria, and hypertension. Cases of HCDD were associated with a CH1 deletion and frequently had hypocomplementemia and a positive hepatitis C virus antibody but negative hepatitis C virus PCR. LCDD & MCN is a morphologically and clinically distinct entity from pure MIDD, presenting with higher creatinine (mean, 7.8 mg/dl; $P = 0.01$), greater dialysis dependence (64 *versus* 26%; $P = 0.053$), subnephrotic proteinuria, and less nodular glomerulopathy (18 *versus* 100%; $P < 0.0001$). Multiple myeloma was more frequently diagnosed in LCDD & MCN than in pure MIDD (91 *versus* 31%; $P = 0.025$). Renal and patient survivals were significantly worse in patients with LCDD & MCN (mean, 4 and 22 mo, respectively), compared with patients with pure MIDD (mean, 22 and 54 mo). Chemotherapy stabilized or improved renal function in 10 of 15 patients (67%) with pure MIDD who presented with creatinine of <5.0 mg/dl, emphasizing the importance of early detection. On multivariate analysis, initial creatinine was the only predictor of renal and patient survival in pure MIDD, underscoring the prognostic significance of the renal involvement.

Nonamyloidotic monoclonal Ig deposition disease (MIDD) is characterized by nodular sclerosing glomerulopathy, proteinuria, renal insufficiency, and an association with dysproteinemias (1). Histologic evaluation reveals monoclonal light- and/or heavy-chain deposits within basement membranes of glomeruli, tubules, and vessels. Three subtypes of MIDD have been reported, including light-chain DD (LCDD) (2–4), light- and heavy-chain DD (LHCDD) (5–6), and heavy-chain DD (HCDD) (7–10). Among these conditions, LCDD is the most prevalent and, in one series, constituted 19% of 118 renal biopsies from patients with multiple myeloma (11). Reports of LHCDD and HCDD are rare, with fewer than 2 dozen documented cases in the literature. HCDD cases have included the full spectrum of γ1, γ2, γ3, γ4, and α-heavy-chain subtypes (7–10,12). A deletion of the CH1 constant domain of the γ-heavy chain underlies the secretion of heavy chains by a lymphocyte or plasma cell clone (13,14).

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At the time of renal biopsy, up to 30% of patients with renal MIDD have no detectable monoclonal protein in serum or urine (1). However, the number of patients who later develop a clinical dysproteinemia is unclear. A retrospective analysis of a small series of 19 patients with LCDD who received chemotherapy (typically melphalan and prednisone) suggested that chemotherapy may stabilize or improve renal function (14). Cases of LHCDD and HCDD are too few to draw conclusions about therapy, although there is a report of a patient whose LHCDD responded to pulse steroids (15).

We reviewed retrospectively 34 renal biopsies processed at Columbia Presbyterian Medical Center from patients with MIDD. The clinical, pathologic, and outcome data from this large series expand the available literature on these important and not infrequent disease entities.

Materials and Methods

Study Design and Patient Selection

The renal pathology files at New York-Presbyterian Hospital, Columbia-Presbyterian Campus, from 1982 to February 2000, were reviewed retrospectively, and 34 cases of LCDD, LHCDD, and HCDD were identified among the 7241 cases (0.47%) processed during this period. Entry into the study was based on the presence of renal biopsy findings diagnostic of MIDD (LCDD, LHCDD, or HCDD). The 34 cases were analyzed with respect to pathologic and clinical findings, as well as outcome data. This information was

obtained mainly by chart review and direct contact with referring physicians.

Pathology Studies

All renal biopsies were processed for light microscopy, immunofluorescence, and electron microscopy according to standard techniques. For each case, 11 glass slides stained with hematoxylin and eosin, periodic acid-Schiff (PAS), trichrome, and Jones methenamine silver were reviewed.

Immunofluorescence was performed on 3-μm cryostat sections by use of a panel of FITC-conjugated rabbit anti-human antibodies to IgG, IgM, IgA, C3, C1, fibrinogen, albumin, and κ and λ light chains (Dako Corporation, Carpenteria, CA). Immunofluorescence staining intensity was graded on a scale of 0 to 3+. For HCDD, γ-chain subtypes were determined by direct immunofluorescence using monoclonal FITC-conjugated antibodies to IgG1 (clone 8c/6 to 39), IgG2 (clone HP6014), IgG3 (clone HP6050), and IgG4 (clone HP6023; The Binding Site, Birmingham, United Kingdom). Frozen sections also were stained with monoclonal antibodies specific for the constant domains (CH1, CH2, and CH3) of IgG heavy chain (clones HP6044, HP6018, HP6016; Centers for Disease Control and Prevention, Atlanta, GA), followed by FITC-conjugated sheep anti-mouse secondary antibody, as described previously (7).

Inclusion criteria were based entirely on pathologic findings. MIDD was defined by immunofluorescence as paraprotein deposits of (*1*) clear monoclonal composition (*i.e.*, staining exclusively for κ or for λ in the case of LCDD, staining for a single class of Ig (γ, μ, or α) with light-chain restriction in the case of LHCDD, or staining for a single class of Ig (γ, μ, or α) with no corresponding light chain in the case of HCDD; (*2*) 2+ or greater intensity of staining; and (*3*) a linear distribution within glomerular and/or tubular basement membranes. The presence of deposits was confirmed subsequently by electron microscopy in all cases of pure MIDD.

Clinical Studies and Laboratory Evaluation

Demographic, clinical, and laboratory information was obtained on each patient at the time of renal biopsy. Follow-up information was obtained on all but two patients. Hypertension was defined as systolic BP >140 or diastolic BP >90 or the use of antihypertensive medications at the time of biopsy. Renal insufficiency was defined as serum creatinine >1.2 mg/dl. Acute renal failure was defined by a 6-mo interval change in serum creatinine of >0.5mg/dl. Nephrotic syndrome was defined as 24-h urinary protein $\geq$3 g/d, edema, and hypoalbuminemia (serum albumin $\leq$3.6 g/dl).

Positive urine protein electrophoresis (UPEP) and serum protein electrophoresis (SPEP) were defined by the presence of a monoclonal (M protein) spike. Hypercalcemia was defined as Ca^{2+} >10.5 mg/dl (corrected for albumin <4.0 g/dl). Positive bone marrow biopsy was defined as $\geq$15% plasma cells. Multiple myeloma (MM) was defined by renal MIDD plus at least one of the following: (*1*) positive bone marrow biopsy, (*2*) presence of osteolytic lesions, (*3*) hypercalcemia with positive UPEP or SPEP, or (*4*) $\geq$10% bone marrow plasmacytosis with low quantitative serum immunoglobulins. Monoclonal gammopathy of unknown significance (MGUS) was defined as presence of MIDD and a positive SPEP or UPEP without other clinical features of myeloma.

At the conclusion of the study, worsening of renal function was defined as a >50% increase in serum creatinine from baseline. End-stage renal disease (ESRD) was defined as serum creatinine $\geq$5.0 mg/dl or dependence on dialysis. Progression to renal failure was defined as ESRD or a doubling of serum creatinine.

Statistical Analyses

Results that involve continuous variables are expressed as mean $\pm$ SEM. For analysis of the clinical and laboratory characteristics between the different groups, nonparametric statistical methods that used exact inference were applied, including the Fisher's exact test, Mann-Whitney *U* test, and Kruskal-Wallis test as appropriate. For analysis of renal and patient survival, Kaplan-Meier estimates were performed. Multivariate analysis was performed by use of logistic regression models and discriminant analysis. Cox regression was used in multivariate analysis of predictors of patient and renal outcome. SPSS for Windows (Version 10.0; SPSS, Inc., Chicago, IL) was used to perform all analyses. Statistical significance was assumed at $P < 0.05$.

Results

Pathology Studies

Renal biopsies from 34 patients met morphologic entry criteria for the diagnosis of MIDD. Twenty-three patients had "pure MIDD" (Figure 1). In 11 cases of LCDD, immunofluorescence also revealed tubular casts staining with high intensity for a single light chain (κ or λ) accompanied by light microscopic findings of atypical, fractured, polychromatic tubular casts, diagnostic of myeloma cast nephropathy (MCN). These 11 cases are classified as combined "LCDD & MCN" (Figure 1).

In all 23 biopsies from patients with pure MIDD, light microscopy revealed a nodular sclerosing glomerulopathy. Glomeruli were enlarged with a diffuse and nodular expansion of the mesangial matrix, often accompanied by mild mesangial hypercellularity (Figure 2A). The mesangial nodules stained PAS positive, trichrome red-blue, and nonargyrophilic. Typically, there was little or no thickening of glomerular basement membranes (GBM). There were occasional membranoproliferative features in the form of circumferential mesangial interposition surrounding some nodules. Global glomerulosclerosis was common, involving a mean of 20% of glomeruli (range, 0 to 81%). Tubular basement membrane (TBM) thickening was

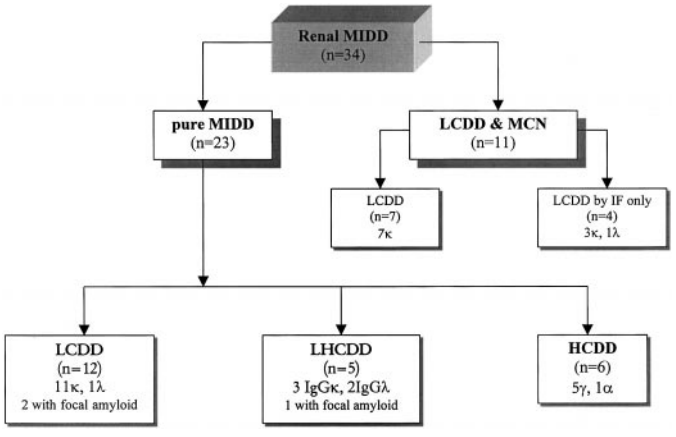

Figure 1. Composition of deposits in 34 cases of monoclonal immunoglobulin deposition disease (MIDD). LCDD, light-chain deposition disease; LHCDD, light- and heavy-chain deposition disease; HCDD, heavy-chain deposition disease; LCDD & MCN, LCDD plus myeloma cast nephropathy.

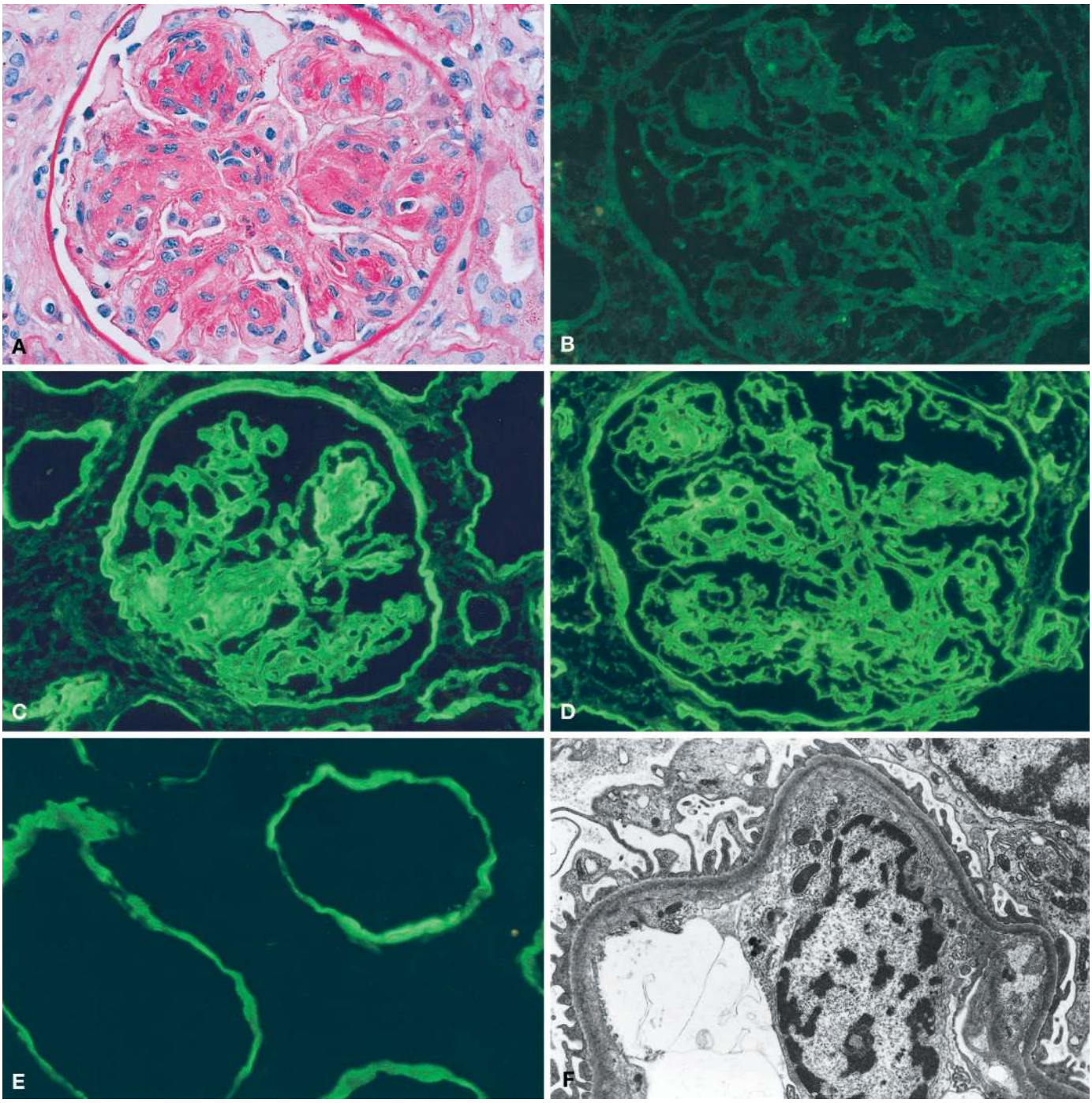

Figure 2. A representative case of HCDD is illustrated. (A) A glomerulus displaying a nodular sclerosing glomerulopathy with global mesangial nodules, some surrounded by mesangial interposition, without obvious thickening of the glomerular basement membranes (GBM). Staining for the constant domains of the γ-heavy chain shows negativity for CH1 (B) and strong linear positivity for CH2 (C) and CH3 (D) along GBM and tubular basement membranes (TBM). Staining for complement component C1 is present along TBM, with a granular to linear texture. Ultrastructural evaluation reveals finely granular electron dense deposits that involve the inner aspect of the GBM. Magnifications: ×400 in A (periodic acid-Schiff), B, C, and D; ×800 in E; ×5000 in F.

variable. The degree of tubular atrophy and interstitial fibrosis ranged from mild in nine cases to severe in eight cases. In some cases, vascular basement membranes surrounding medial myocytes were thickened by PAS-positive material. Congo red staining for amyloid was performed in all cases; in 3 of the 23 cases (all κ), there was focal positivity consistent with superimposed amyloidosis, which was confirmed by the demonstration of 8- to 12-nm fibrillar deposits on electron microscopy. Nonetheless, the dominant finding was MIDD, and, therefore, these three cases were included in the group of pure MIDD for purposes of analysis. Two cases also displayed overlapping features of diabetic nephropathy.

The following patterns of paraprotein deposition were identified by immunofluorescence: among the 12 cases of pure LCDD, the dominant light chain was κ in 11 cases and λ in 1 case. The five cases of LHCDD included three with IgGκ and two with IgGλ. The six cases of HCDD included γ-heavy chain in five cases and α-heavy chain in one case. Tissue was available for further study in four cases of γ HCDD, and among these cases, the heavy-chain component was identified as γ1 in two cases, γ3 in one case, and γ4 in one case. Furthermore, in all four cases, a deletion of the CH1 constant domain of the γ-chain was identified by immunostaining (Figure 2, B through D). In two of the five cases of LHCDD and in four of the five cases of γ HCDD, the monoclonal deposits fixed complement components C3 and C1 in a granular or linear pattern (Figure 2E). Complement fixation was identified in the three cases with γ1 or γ3 heavy chains but not in the case with γ4 heavy chain.

In all cases of MIDD, immunofluorescence revealed linear deposits within TBM. In addition, GBM deposits were identified in 20 of 23 cases (87%), mesangial deposits in 19 of 23 (83%), interstitial deposits in 7 of 23 (30%), and vascular deposits in 15 of 23 (65%). None of the 23 cases of pure MIDD displayed significant monoclonal staining of tubular casts or other histologic evidence of MCN.

Ultrastructural evaluation of the 23 cases of pure MIDD demonstrated deposits in GBM (100% of cases), mesangium (96%), and TBM (96%) (Figure 2F). The deposits typically appeared to be granular-powdery and were identified in the lamina rara interna and/or permeating the lamina densa of the GBM. Interstitial deposits also were identified in a minority of cases (18%). In the 18 cases in which vessels were sampled for electron microscopy, deposits commonly were seen surrounding the basement membranes of individual myocytes (78%). The degree of foot process fusion was variable but typically extensive (mean, 55%; range, 5 to 100%).

The appearance of the 11 cases of combined LCDD & MCN differed significantly from those with pure MIDD. The major light microscopic findings were those of atypical, fractured, polychromatic casts, typical of MCN, associated with interstitial edema, inflammation, fibrosis, and diffuse tubular degenerative changes (Figure 3A). Although a nodular sclerosing glomerulopathy was seen in all cases of pure MIDD, this

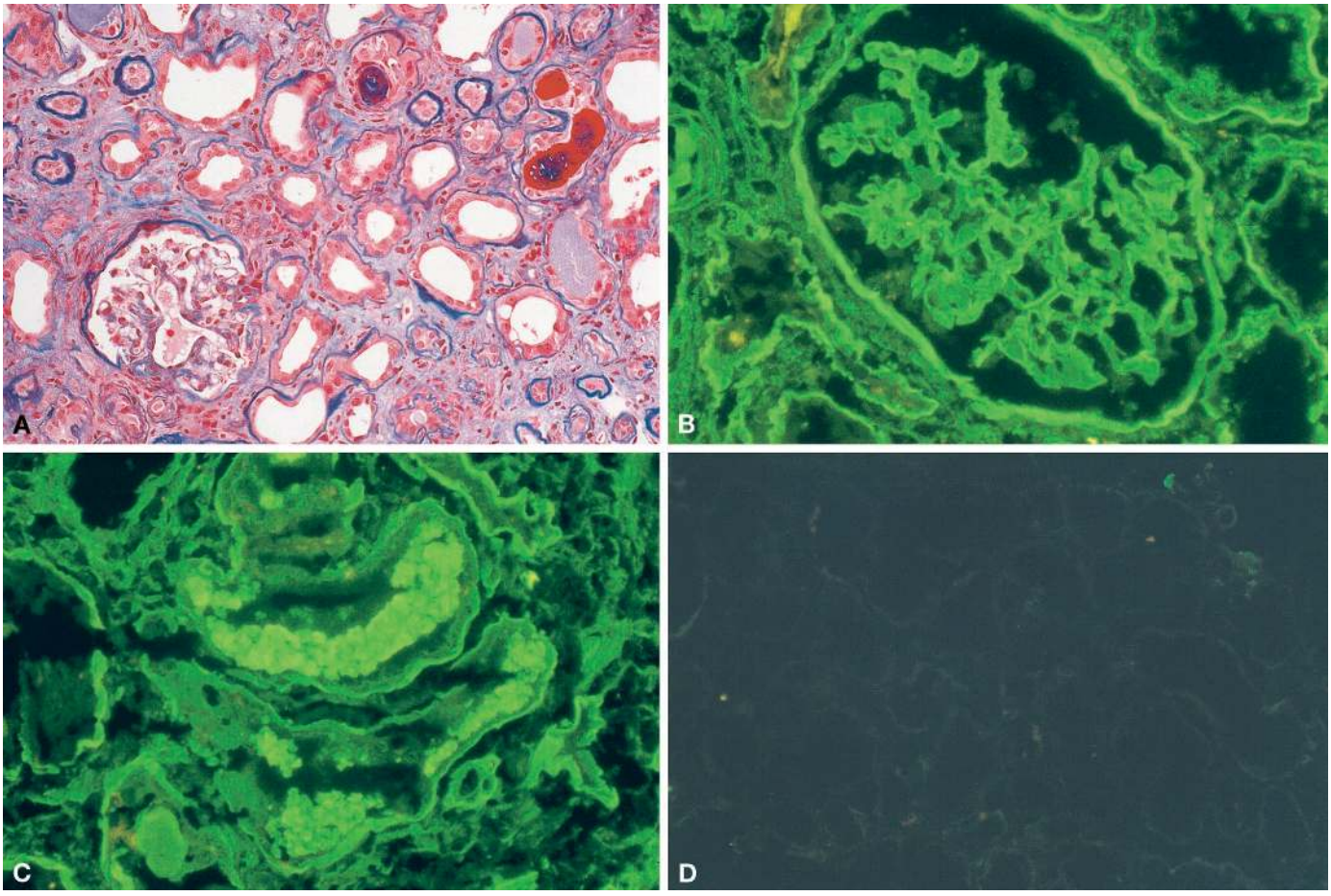

Figure 3. A representative case of LCDD & MCN. (A) A low-power view that shows focal hard polychromatic casts, diffuse tubular degenerative changes, and interstitial fibrosis, typical of MCN. A glomerulus appears normal by light microscopy. (B) Although glomeruli display no abnormalities by light microscopy, immunofluorescence staining for κ reveals intense linear staining of GBM and TBM, typical of LCDD. In addition to linear TBM staining, there is strong staining of the atypical casts for κ (C) and complete negativity for λ (D). Magnifications: ×200 in A (trichrome); ×400 in B; ×800 in C and D.

pattern of disease was seen in only 2 of the 11 cases of LCDD & MCN (18%; $P < 0.0001$). Two additional cases displayed mild mesangial expansion, whereas in seven cases, glomeruli appeared histologically unremarkable. By immunofluorescence, the monoclonal light chain was κ in 10 cases and λ in 1 case. Paraprotein deposits were identified in all cases within GBM and TBM and in the majority of cases (82%) within vessel wall basement membranes (Figure 3B). In all cases, immunofluorescence also revealed the diagnostic finding of MCN: large, fractured casts that stain intensely with a single light-chain component (Figure 3, C and D).

The cases of combined LCDD & MCN were subdivided further into two subgroups, depending on whether electron-dense deposits were identified. Four cases had monoclonal light-chain staining by immunofluorescence but no corresponding electron-dense deposits by electron microscopy. Accordingly, the findings in these four cases are referred to as "LCDD & MCN (by IF only)." Among the seven cases of LCDD & MCN, electron-dense deposits were identified in GBM in all seven cases and in the mesangium and TBM in six cases. Typically, the extent of GBM and mesangial deposits was less than that in pure MIDD, and only mild foot process fusion was identified (mean, 23%; range, 10 to 40%).

Clinical Characteristics at Biopsy: Demographics and Renal Presentation

The 23 patients with pure MIDD consisted of 12 men and 11 women with a mean age of 57.4 yr (Table 1). A total of 74% were Caucasian, and 5 of 23 (22%) were African American; notably, among the 5 African American patients, 4 had heavy-chain deposition (either HCDD or LHCDD). There was a trend toward greater age in the group with LCDD & MCN, compared with those with pure MIDD (67.1 *versus* 57.4 yr; $P = 0.066$); however, racial composition and gender were not significantly different. Hypertension was present in the majority of cases but was seen less frequently in patients with LHCDD (40%) than in those with LCDD (83%) or HCDD (100%) ($P = 0.03$). Four patients (12%) had a clinical history of type 2 diabetes mellitus, but only two had biopsy findings suggestive of diabetic nephropathy.

With the exception of one case of *de novo* LCDD in a renal allograft, all other cases of MIDD were diagnosed in the native kidney. Patients with pure MIDD typically presented with renal insufficiency at the time of biopsy, as evidenced by 96% with serum creatinine >1.2 mg/dl (Table 1). Patients with LCDD & MCN had a significantly higher serum creatinine (7.8 *versus* 4.5 mg/dl; $P = 0.01$) and a lower creatinine clearance (13.8 *versus* 37.3 cc/min; $P = 0.02$) when compared with the group with pure MIDD.

Nephrotic-range proteinuria was seen in almost half (48%) of patients with pure MIDD, and the mean 24-h urine protein was 4.2 g/d. In contrast, the mean 24-h proteinuria was significantly less in patients with LCDD & MCN (2.2 g/d; $P = 0.01$), and nephrotic-range proteinuria was seen in only 2 of 11 patients (18%). Furthermore, the degree of hypoalbuminemia and hypercholesterolemia and the incidence of peripheral edema were greater in patients with pure MIDD, such that full nephrotic syndrome was present in 6 of 23 cases but in none of the 11 patients with LCDD & MCN. Hypocomplementemia was present in one of five patients with LHCDD and in three of six patients with HCDD.

Among patients with pure MIDD, the incidences of acute renal failure and dialysis dependence (at the time of biopsy) were 30 and 26%, respectively. These incidence rates were significantly lower than in patients with LCDD & MCN, of whom 82% had acute renal failure and 64% required dialysis ($P = 0.02$ and $P = 0.053$, respectively).

Of note, five of six HCDD patients who were tested for hepatitis C virus (HCV) antibody by second generation enzyme immunoassay were positive, whereas none of the eight patients with LCDD or four patients with LCDD & MCN studied were HCV antibody positive ($P < 0.001$). All five patients' bilirubin and serum transaminase were within the normal range, and four were HCV PCR negative. HCV data were not available for any patients with LHCDD.

Oncologic Characteristics

Renal biopsy diagnosis of MIDD preceded any other clinical evidence of dysproteinemia in 16 patients (70%) with pure MIDD and in 7 patients (64%) with LCDD & MCN (Table 2). In only 11 of 34 patients was an M spike tested and identified on SPEP and/or UPEP before biopsy. After renal biopsy diagnosis of pure MIDD, an M spike was identified on SPEP in 48% and on UPEP in 52%; in 3 of 23 patients with pure MIDD (13%), both SPEP and UPEP (and immunofixation) were negative. A positive SPEP was present in 80% of patients with LHCDD, compared with 25% of patients with LCDD ($P = 0.04$) and 67% of patients with HCDD.

Oncologic workup of patients with pure MIDD revealed a positive bone marrow biopsy in 35%, hypogammaglobulinemia in 30%, osteolytic lesions in 13%, and hypercalcemia in a single patient (4.3%). Thirty-nine percent of patients with pure MIDD met criteria for MM, and 39% were diagnosed with MGUS. At presentation, the only oncologic parameter that differed significantly between the pure MIDD and LCDD & MCN groups was the higher incidence of multiple myeloma in the latter (39 *versus* 91%; $P = 0.025$).

Outcome

Among the seven patients with LCDD and MM, four were treated with melphalan and prednisone (MP) and one each with regimens of vincristine-adriamycin-dexamethasone; steroids; and vincristine, cyclophosphamide, and MP. At follow-up (mean, 31.5 mo), five had stable renal function, one developed an increase in serum creatinine from 1.5 to 2.3 mg/dl over 47 mo, and one progressed to ESRD requiring hemodialysis. Four of the seven patients with LCDD and MM died during the follow-up period; exact causes of death are not known. In contrast, the two patients with LCDD and MGUS were treated with MP and plasmapheresis, respectively, and both remain alive at 24 and 27 mo. One patient progressed from a serum creatinine of 2.9 mg/dl to dialysis dependence over 24 mo, whereas the other had an increase in serum creatinine from 6.2 to 6.7 mg/dl over 27 mo but has not yet required dialysis. The

Table 1. Demographics and renal presentation[a]

Characteristic	LCDD (n = 12)	LHCDD (n = 5)	HCDD (n = 6)	Pure MIDD (n = 23)	LCDD & MCN (n = 11)	P Value
Gender (M/F)	7/5	2/3	3/3	12/11	5/6	NS
Age (yr)	56.6 ± 2.87	63.8 ± 5.88	53.8 ± 2.63	57.4 ± 2.12	67.1 ± 3.92	0.066[b]
Hypertension	10 (83%)	2 (40%)	6 (100%)	18 (78%)	7 (64%)	0.03[c]
Creatinine (mg/dl)	4.0 ± 0.9	5.3 ± 2.0	4.8 ± 1.5	4.5 ± 0.7	7.8 ± 1.2	0.01[b]
Renal insufficiency (sCr ≥1.2 mg/dl)	11 (92%)	5 (100%)	6 (100%)	22 (96%)	11 (100%)	NS
Proteinuria (g/24 h)	4.2 ± 0.8	2.9 ± 1.0	5.3 ± 2.2	4.2 ± 0.7	2.2 ± 0.7	0.01[b]
Nephrotic proteinuria (≥3 g/24 h)	6 (50%)	1 (20%)	4 (67%)	11 (48%)	2 (18%)	NS
Albumin (g/dl)	3.6 ± 0.2	2.8 ± 0.2	2.9 ± 0.3	3.2 ± 0.2	3.6 ± 0.2	NS
Cholesterol (mg/dl)	275.4 ± 17.2	215 ± 12.1	212.5 ± 26.7	246.3 ± 14.0	218 ± 23.1	0.05[d]
Edema	5 (42%)	5 (100%)	5 (83%)	15 (65%)	2 (18%)	0.01[b]
Nephrotic syndrome	2 (17%)	1 (20%)	3 (50%)	6 (26%)	0 (0%)	NS
Microhematuria (>5 RBC/hpf)	5 (42%)	3 (60%)	4 (67%)	12 (52%)	4 (36%)	NS
Hypocomplementemia	0 (0%)	1 (20%)	3 (50%)	4 (17%)	0 (0%)	NS
Acute renal failure	4 (33%)	1 (20%)	2 (33%)	7 (30%)	9 (82%)	0.02[b]
Dialysis at time of biopsy	2 (16%)	2 (40%)	2 (33%)	6 (26%)	7 (64%)	0.053[b]

[a] Results are given as no. (%) or mean ± SEM. NS, not significant; HTN, hypertension; LCDD, light-chain deposition disease; LHCDD, light- and heavy-chain deposition disease; HCDD, heavy-chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; RBC, red blood cells; hpf, high-power field.

[b] Pure MIDD *versus* LCDD & MCN.

[c] LHCDD *versus* LCDD & HCDD.

[d] LCDD *versus* LHCDD & HCDD.

Table 2. Oncologic findings and clinical outcomes[a]

Findings and Outcomes	LCDD (n = 12)	LHCDD (n = 5)	HCDD (n = 6)	Pure MIDD (n = 23)	LCDD & MCN (n = 11)	P Value
Known M spike prior to bx	2 (17%)	4 (80%)	1 (17%)	7 (30%)	4 (36%)	NS
(+) SPEP[e]	3 (25%)	4 (80%)	4 (67%)	11 (48%)	3 (27%)	0.04[c]
(+) UPEP[e]	5 (42%)	4 (80%)	3 (50%)	12 (52%)	7 (64%)	NS
(−) UPEP AND (−) SPEP[e]	2 (17%)	0 (0%)	1 (17%)	3 (13%)	1 (9%)	NS
Serum immunofixation[f]	1κ, 4IgGκ, 5 nl 1 decr γ and 1 incr α	2 IgGκ, 1 IgGλ 2 unknown	1 IgGκ, 3 low γ 1 IgAκ and 1 IgMλ		1IgGκ, 1κ, 5 nl, 2 γ spike, 1 decr γ 1 unknown	
Hypogammaglobulinemia	5 (42%)	0 (0%)	2 (34%)	7 (30%)	5 (45%)	NS
(+) BM biopsy ≥15% plasma cells	6 (50%)	2 (40%)	1 (17%)	8 (35%)	8 (73%)	NS
(+) Skeletal survey	2 (17%)	0 (0%)	1 (17%)	3 (13%)	1 (9%)	NS
Corrected Ca^{2+} >10.5 mg/dl	0 (0%)	1 (20%)	0 (0%)	1 (4.3%)	3 (27%)	NS
Clinical diagnosis[b]						
multiple myeloma	7 (58%)	1 (20%)	1 (17%)	9 (39%)	10 (91%)	0.025[d]
MGUS[b]	2 (17%)	3 (60%)	4 (66%)	9 (39%)	0 (0%)	
isolated HCDD	0 (0%)	0 (0%)	1 (17%)	1 (4%)	0 (0%)	
insufficient data	3 (25%)	1 (20%)	0 (0%)	4 (17%)	1 (9%)	
Mean follow-up time (mo)	33.2 ± 9.5	9.1 ± 5.1	14.8 ± 6.6	22.6 ± 5.6	14.7 ± 3.4	
range (mo)	(7–99)	(1–27)	(2–42)	(1–99)	(0.2–36)	
Renal outcome						0.057[d]
ESRD/dialysis at presentation	3 (25%)	2 (40%)	3 (50%)	8 (35%)	9 (82%)	0.053[d]
stable/improved[b]	5 (42%)	2 (40%)	3 (50%)	10 (43%)	1 (9%)	
worsening renal function[b]	1 (8%)	1 (20%)	0 (0%)	2 (9%)	0 (0%)	
progression to ESRD/dialysis[b]	3 (25%)	0 (0%)	0 (0%)	3 (13%)	1 (9%)	
ESRD/dialysis at study end	6 (50%)	2 (40%)	3 (50%)	11 (48%)	10 (91%)	0.063[d]
Mean time to ESRD (mo)	27	8	3	22	4	0.0196[d]
Mean time to death (mo)	69	13	42	54	22	0.05[d]/0.01[c]
Patient deaths	6 (50%)	3 (60%)	1 (17%)	10 (43%)	6 (55%)	NS

[a] Results are given as no. (%) or mean ± SEM. BM, bone marrow; UPEP, urine protein electrophoresis; SPEP, serum protein electrophoresis; MCN, myeloma cast nephropathy; MGUS, monoclonal gammopathy of unknown significance; ESRD, end-stage renal disease; nl, normal.
[b] Defined in Materials and Methods section.
[c] LCDD *versus* LHCDD.
[d] Pure MIDD *versus* LCDD & MCN.
[e] After renal biopsy diagnosis.
[f] At any time during clinical course.

three patients with LCDD and insufficient data for oncologic diagnosis all required dialysis within 1 mo of presentation.

Follow-up data were available on all five patients with LHCDD, of which two received MP and one received cyclophosphamide and prednisone. Information on treatment was not available for two patients. Renal function remained stable in two patients (one of whom met criteria for MM), one had a worsening of renal function, and two already required dialysis at the time of presentation. Follow-up time is limited to 9.1 mo in the LHCDD group, in part because of the early death of three of the five patients.

Among the six cases of HCDD, the only patient who met criteria for MM was the single patient with α-HCDD. This patient was not treated, and renal function remained stable at 2-mo follow-up. The remaining five patients received either MP (one patient), pulse decadron (one patient), prednisone plus chlorambucil (one patient), or no treatment (two patients). Follow-up data revealed two patients with stable serum creatinine (over 5 mo each) and three who presented with either ESRD or immediate requirement for dialysis. Of interest, the single patient who received pulse decadron had an initial increase in serum creatinine from 1.6 to 2.2 mg/dl over 1 mo, followed by a decrease to 1.0 mg/dl at the end of 5 mo. At last follow-up (mean, 14.8 mo), all six patients with HCDD were alive. One patient with HCDD received a living related renal transplant from her sister and is doing well 8 mo posttransplantation without recurrence of proteinuria.

Ten of the 11 patients with LCDD & MCN met clinical criteria for the diagnosis of MM. Four of the patients received MP, five patients received vincristine-adriamycin-decadron (four also received MP, prednisone, cyclophosphamide, or thalidomide), and one was treated solely with steroids. Eight of the 10 patients presented with ESRD without subsequent recovery, and 1 patient had an increase in serum creatinine from 2.6 to 6.8 mg/dl over 2 mo. Of interest, a single patient with MM who was treated with MP had a decline in serum creatinine from 3.5 to 2.0 mg/dl over 36 mo. The single patient with insufficient data to establish an oncologic diagnosis required dialysis at the time of presentation. At last follow-up (mean, 14.7 mo), 6 of the 11 patients with LCDD & MM had died. Causes of death included sepsis (two patients), hypercalcemia (one patient), and progressive myeloma (three patients).

Renal ($P = 0.0196$) and patient ($P = 0.0453$) survivals were significantly better in patients with pure MIDD *versus* LCDD & MCN (Figures 4 and 5). Improvement in renal function was seen in 10 of 23 patients with pure MIDD (43.5%) but only in a single patient with LCDD & MCN (9.1%; $P = 0.0487$). When patients were reanalyzed for the presence of clinical criteria for MM, 10 of 19 patients with MM (52.6%) died at the end of the study, as opposed to 2 of 10 (20%; $P = 0.0956$) who had been diagnosed with MGUS. Median patient survival time was 36 mo in the MM group and 42 mo in the MGUS group ($P = 0.74$). Mean patient survival in LCDD was 69 *versus* 13 mo in LHCDD *versus* 42 mo in HCDD, with a statistically significant difference between the LCDD and LHCDD groups ($P = 0.01$). The end points of progression of renal insufficiency or ESRD were not significantly different among the three groups (27 mo in LCDD *versus* 8 mo in LHCDD *versus* 3 mo in HCDD;, $P = 0.34$) when adjusted for the relatively

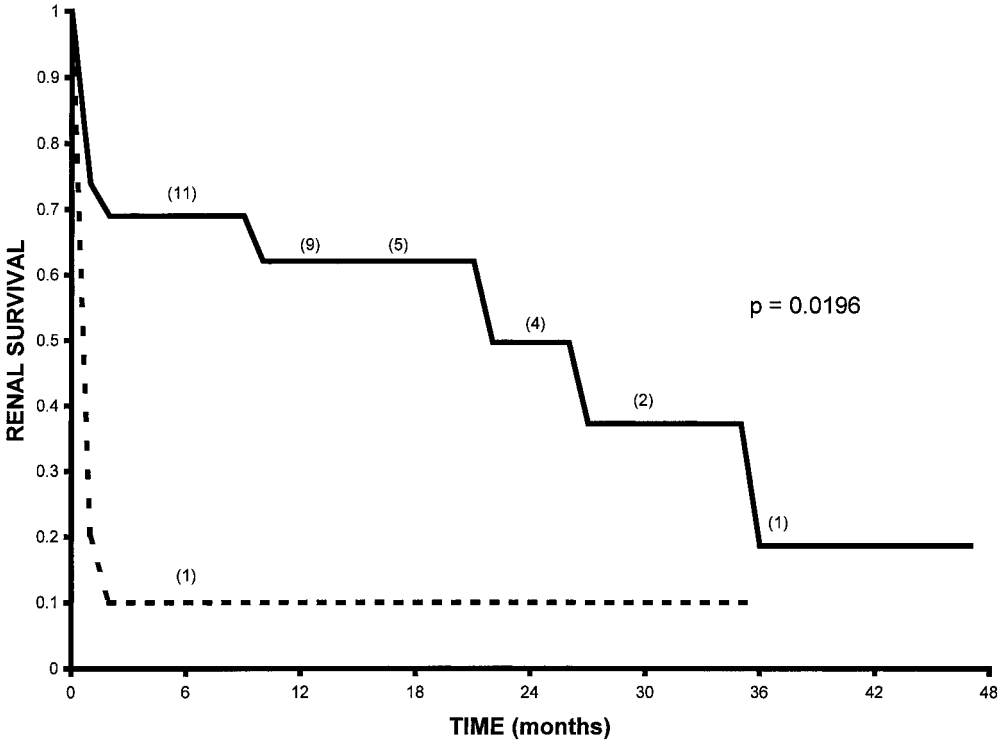

Figure 4. Life-table analysis of renal survival in pure MIDD *versus* LCDD & MCN. Solid line, pure MIDD; dotted line, LCDD & MCN.

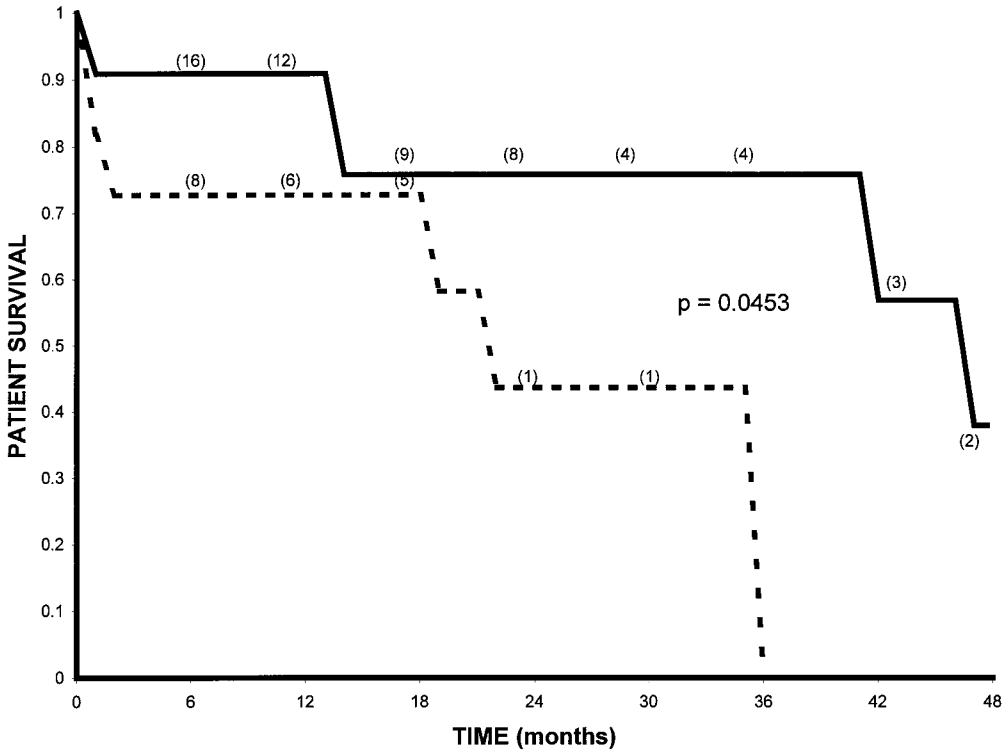

Figure 5. Life-table analysis of patient survival in pure MIDD *versus* LCDD & MCN. Solid line, pure MIDD; dotted line, LCDD & MCN.

short follow-up time in the LHCDD (mean, 9.1 mo) and HCDD (mean, 15.7 mo) groups.

Limited follow-up data are available regarding proteinuria. Among the five patients with LCDD and stable/improved renal function, proteinuria declined in two, increased in one, and was unavailable in the remaining two patients. In the four patients with either LHCDD or HCDD and stable renal function, a decline in proteinuria was seen.

On multivariate analysis of the pure MIDD group, there was no correlation between renal or patient survival and any histologic parameter, including severity of glomerulosclerosis, interstitial inflammation, interstitial fibrosis, tubular atrophy, or vascular disease. Oncologic diagnosis and treatment also did not correlate with either renal or patient survival. The only predictor of renal and patient survival was the initial serum creatinine at the time of biopsy ($P = 0.003$ and 0.042, respectively).

Discussion

We report the clinical, pathologic, and outcome data in a large series of patients with renal MIDD. MIDD is a paraprotein deposition disease characterized by monoclonal deposits within renal basement membranes, indicative of underlying plasma cell dyscrasia. However, not all cases have a demonstrable monoclonal protein by SPEP or UPEP.

One third of our 34 cases of MIDD had evidence of coexistent MCN. The pathologic findings in these 11 cases of LCDD & MCN were dominated by the MCN component and manifested severe tubular damage by cast nephropathy, with less extensive glomerular pathology. Although linear deposits were noted in basement membranes by immunofluorescence in all 11 cases, they typically were less extensive than in pure MIDD. Furthermore, in 4 of the 11 cases, corresponding electron-dense deposits were not identified by electron microscopy (LCDD & MCN [by IF only]). Potential explanations for this finding include nonspecific "trapping" of the circulating monoclonal light chain in renal basement membranes reflecting high serum levels without true deposit formation or insufficient aggregation of the deposits to be visualized at the ultrastructural level. LCDD & MCN tended to occur in older patients who presented with more severe renal insufficiency and less severe proteinuria and were more likely to fulfill criteria for MM. The clinical, pathologic, and outcome data of this group are more typical of MCN than MIDD. Unfortunately, past studies of LCDD have not always distinguished between pure MIDD and cases with overlapping MCN. For example, Ganeval *et al*. (4) and Buxbaum *et al*. (5) each reported series of LCDD in which almost 50% of patients had concurrent cast nephropathy, but they did not perform subgroup analysis.

Examination of the histologic findings in patients with MIDD reveals multiple interesting trends. κ is the predominant light chain deposited within renal basement membranes in LCDD, as identified in 91% of our cases, and is similar to the reported incidences of 73 to 87.5% in other series (2–5,15). This is in clear contrast to the increased λ-to-κ ratio seen in amyloidosis and correlates with the reported predominance of Vκ4 and Vλ6 as precursor proteins in LCDD and amyloidosis, respectively (16,17). Among cases of HCDD, γ is the predom-

inant class of heavy chain. Our single case of α-HCDD is the second such case reported (10). A CH1 deletion was noted in all four of our γ-HCDD cases studied, correlating with the previous finding that this deletion is critical for premature heavy-chain secretion by plasma cell clones (13,18). Although a nodular sclerosing glomerulopathy is the most common finding on light microscopy in MIDD, its incidence ranges from 31 to 74% (2–5,15). We identified this pattern in only 2 of 11 cases of LCDD & MCN, possibly because of their early presentation with MCN-induced acute renal failure, with insufficient time for the development of nodular sclerosing glomerulopathy. Alternatively, the pathogenic light-chain proteins in this entity may be less sclerogenic, as suggested by their variable ability to upregulate mesangial synthesis of TGFβ (19). If all previously reported LCDD cases with overlapping MCN are excluded, the true incidence of nodular sclerosing glomerulopathy in pure MIDD likely would approach the 100% found in our series. Similarly, in our series, deposits were readily identified by immunofluorescence or electron microscopy in GBM (87 and 100%, respectively), mesangium (83 and 96%), TBM (100 and 96%), and vessel wall basement membranes (65 and 78%). Our rate of detection of deposits was higher than that in previous studies of MIDD (2–5,15), likely because of our exclusion of cases in which MCN dominated. Despite the broad pathologic spectrum of MIDD, no morphologic parameter was found to be predictive of renal or patient survival in our series, as noted in a previous analysis (2).

MIDD typically presents in the sixth decade, although, in our cohort, an earlier age of presentation was seen in patients with pure MIDD than in those with LCDD & MCN. The typical renal presentation in patients with MIDD includes proteinuria, hypertension, and renal insufficiency. We identified renal insufficiency in 96% of patients with pure MIDD, compared with 92% of cases compiled from five previous series (2–5,15). Nephrotic range proteinuria ($\geq$3 g/d) was present in 48% of patients in our cohort, compared with 57% in previous series (2–5,15). Of interest, hypocomplementemia was present in three of our six patients with HCDD, all of whom had heavy-chain deposits composed of γ1 or γ3. These results are consistent with the known complement-fixing ability of these γ subclasses, a property that is dependent on an intact CH2 domain.

Consistent with previous literature, the incidence of overt MM was greater in patients with LCDD & MCN than in those with pure MIDD (91 *versus* 39%; $P = 0.025$). Previous series revealed a 45% incidence of MM at presentation, likely because of the inclusion of cases with combined LCDD & MCN (2–5,15). Three of our 23 patients (13%) and 11 of 64 previously reported cases (17%) had no evidence of a monoclonal spike on either SPEP or UPEP (2–5,15), which indicates that the absence of such laboratory findings does not exclude a diagnosis of MIDD.

Analysis of treatment and outcome data is hampered by the small patient numbers, failure of some series to separate the subgroup with concurrent MCN, lack of standardized therapy, and limited follow-up. The majority of patients received steroids plus melphalan or a cytotoxic agent. It is general practice to treat patients who have pure MIDD or LCDD & MCN with similar regimens, irrespective of whether they meet diagnostic criteria for myeloma. Although renal prognosis is poor, patient survival can be considerable, with 70% and 37% 5-yr patient and renal survivals reported in one series (14). In our cohort, among patients with pure MIDD, 35% presented with ESRD, 22% had worsening of renal function or progression to ESRD, and 43% had stable or improved renal function. No patient who presented with ESRD or requiring dialysis improved; however, 10 of the remaining 15 patients (67%) with pure MIDD had stable or improved renal function at the end of a mean follow-up of 23.7 mo. Unfortunately, no conclusions could be drawn regarding the relative efficacy of the varied treatment regimens. Of interest, the presence of MM did not influence renal or patient survival. This is consistent with our observation that the only predictor of renal and patient survival was the initial serum creatinine at the time of biopsy, which underscores the paramount prognostic importance of renal MIDD.

An interesting and previously unreported finding was that of a positive HCV antibody test with undetectable HCV by PCR in four of five patients with HCDD studied. None of the patients had elevated bilirubin or transaminase to suggest active hepatitis. These findings may represent a false-positive HCV antibody test because of interference by the abnormal truncated heavy chains with the HCV immunoassay; a distant HCV infection also is possible.

In summary, MIDD is defined by linear deposits of monoclonal light-chain components in renal basement membranes, often producing a nodular sclerosing glomerulopathy. Because fewer than half of patients with MIDD have clinical or laboratory features of MM, renal biopsy plays an essential role in the diagnosis of dysproteinemia. Accurate histopathologic diagnosis requires, above all, a systematic analysis of the immunofluorescence findings. Approximately one third of cases have overlapping features of MCN; this subgroup is distinguished by greater renal insufficiency and less proteinuria at presentation, a renal biopsy picture typically dominated by MCN, and poorer renal and patient outcomes. Because this group more closely resembles that of MCN, it should be segregated from future analyses of pure MIDD. Although patient and renal survival rates remain poor, with early detection and treatment, stable or improved renal function may be achieved (4,14,20). In the future, large multicenter studies of MIDD will be needed to determine the optimal mode of therapy.

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