Light Chain Deposition Disease: A Model of Glomerulosclerosis Defined at the Molecular Level

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Because the renal plasma flow represents 20% of the total plasma flow and the glomerulus is the renal filtering unit continuously exposed to plasma proteins, the glomerulus is a prominent target for deposition of abnormal proteins or proteins with a peculiar affinity for constituents of the capillary wall. Among these proteins, monoclonal Ig or their heavy-chain (HC) or light-chain (LC) subunits are responsible for a wide spectrum of glomerular diseases that can be classified into two categories by electron microscopy (Table 1). The first category is those with organized deposits and includes diseases with fibril formation, mainly amyloidosis, and diseases with microtubule formation, including cryoglobulinemic kidney and immunotactoid glomerulonephritis. Only amyloid deposits stain for Congo red, a tinctorial property related to the B-pleated sheet organization of amyloid fibrils common to all forms of amyloid. The second category of diseases is characterized by nonorganized electron-dense granular deposits. They are localized in basement membranes in most tissues, especially the kidney, and define a disease now called monoclonal Ig deposition disease (MIDD) (1,2), a term that by convention excludes Ig-derived amyloidosis. MIDD differs from amyloidosis by the lack of affinity for Congo red. The distinction between amyloid light-chain (AL) amyloidosis and MIDD also is justified by the different pathophysiology of amyloid that implicates one-dimensional elongation of a pseudocrystalline structure and MIDD that involves nonorganized amorphous precipitation of Ig chains (see Pathogenesis section).

History

It was known from the late 1950s that nonamyloidotic forms of glomerular disease resembling diabetic glomerulosclerosis could occur in multiple myeloma (3,4). The presence of monoclonal LC in these lesions was recognized in 1973 by Antonovych et al. (5) and confirmed by Randall et al. (6), who published in 1976 the first description of LC deposition disease (LCDD). Although the deposits in AL amyloidosis contain monoclonal LC or LC fragments, the term light-chain deposition disease is used only for the disease that features nonamyloid electron-dense granular deposits as described by Randall et al. (6). Monoclonal HC were found together with LC in the tissue deposits from certain patients (6,7), and the term light- and heavy-chain deposition disease (LHCD) (1) was proposed. More recently, deposits containing monoclonal HC in the absence of detectable LC were observed in patients who were affected by otherwise typical Randall’s disease (heavy-chain deposition disease [HCDD]) (8), and the first series of four patients was reported in 1999 (9).

Pathogenesis

At variance with amyloidosis, lesions in MIDD are related clearly to accumulation of extracellular matrices (ECM). The Ig chains that are responsible for this effect display peculiar structural properties and proneness to precipitate in certain extracellular areas where they most likely stimulate ECM production.

Ig Chain Structure

Ig are made up of two pairs of subunits: two HC and two LC, each of which includes a variable domain implicated in antigen recognition, and a constant region that itself includes one or several domains and that activates a variety of effector systems. Binding to antigen and activating effector cells or complement (i.e., antibody function) is made possible by the association of two HC and two LC. LC may be of κ or λ type, with one constant and one variable domain (termed Ck and Vκ). HC may be of nine isotypes (μ, γ1, γ2, γ3, γ4, α1, α2, δ, and ε) that define Ig classes and subclasses: IgM, IgG (including IgG1 to IgG4), IgA (including IgA1 and IgA2), IgD, and IgE. HC include from the −NH2 to the −COOH terminus one variable domain (VH) from a common repertoire for all isotypes and three (for IgG, IgA, and IgD) or four (for IgM and IgE) constant domains, termed Ck1 to Ck4 (see Figure 1).

Normal Ig display a striking structural heterogeneity that is borne essentially by the variable domains and is related to the
diversity of the antigenic determinants that they are supposed to recognize. These regions of the Ig chains are encoded by numerous gene segments, the rearrangement of which occurs during B-cell differentiation and is mandatory for Ig production. Comparison of VH and VL sequences allowed definition of variability subgroups on the basis of their homologies: HC express six VH subgroups, k chains express four VK subgroups, and \( \lambda \) chains express six VL subgroups. The variability of VH and VL is even higher in three small peptidic portions called complementarity determining regions (CDR1, CDR2, and CDR3) that form three loops at one end of the domain that constitutes the antibody binding site.

At variance with normal polyclonal Ig, monoclonal Ig are secreted by a single clone of differentiated B cells that expands excessively, either in a tumoral context (myeloma, Waldenström’s disease, etc.) or without patent hematologic malignancy (monoclonal gammopathy of undetermined significance). A monoclonal Ig may be secreted as free LC (or rarely, HC) that displays structural anomalies causing tissue deposition.

**Abnormal Structures of LC Variable Domains**

In LCDD, isotype restriction is significant; \( \kappa \) chains occur in approximately 80% of cases. This contrasts with the increased \( \lambda \) to \( \kappa \) ratio seen in amyloidosis. Data on N-terminal sequences of the LC from six consecutive patients with LCDD suggested an overrepresentation of the rare VKIV variability subgroup (10). This subgroup features a longer CDR1 loop that contains some hydrophobic residues. The role of LC variable region (VL) in LC deposition is suggested by the fact that amino acid changes in VL were sufficient to promote tissue deposition in mice that expressed a human LCDD VKIV chain (11).

The primary structures of a few additional LCDD precursors were analyzed at the cDNA (12,13) and protein levels (14). As in AL amyloidosis, no common structural motif emerged from these studies. The most remarkable observations were unusual hydrophobic residues at positions where they either could be exposed to the solvent or strongly modify the conformation, especially in the CDR (13,14). In particular, molecular modeling experiments performed on VKI and VKIV LC underline the presence of leucine, isoleucine, or tyrosine at positions 27 and/or 31 in all known cases of LCDD. Other nonpolar groups may be exposed on CDR regions, which suggests that hydrophobic interactions are important either in the amorphous precipitation of LC or in the mechanisms that lead to overproduction of ECM components (15). Of note, in contrast to LCDD LC, those involved in AL amyloidosis often present particular acidic residues in CDR and might form fibrils through electrostatic interactions.

When pathogenic LC could not be detected in the serum and urine, which occurred in 15 to 30% of patients, they seemed to be N-glycosylated in all tested cases (10,16). In vitro biosynthetic labeling experiments on short-term cultures showed that LC that were absent in the urine actually were secreted by the bone marrow plasma cells (1,17,18). Thus, together with the presence of hydrophobic residues, glycosylation might increase the LC propensity to precipitate in tissues and displace the equilibrium from soluble toward deposited amorphous forms.

**Truncated HC**

Twenty-two cases of HCDD have been reported (19 and reviewed in reference 20). In all patients, a monotypic HC without LC was detected in the deposits. A deletion of the C\(_{H1}\) domain was found in the deposited or circulating HC in the 10 patients with \( \gamma \) HCDD where it was searched for. It also was suggested in a patient with \( \alpha \) HCDD (21). Deletions of the C\(_{H1}\), hinge, and C\(_{H2}\) domains were found in one case (8).

The loss of the C\(_{H1}\) domain suggests that secretion of the free, abnormal HC is required for tissue deposition. Normal
HC associate posttranslationally with Ig binding protein (BIP) in the endoplasmic reticulum. The LC later assemble with HC, and the complex is transferred to the Golgi apparatus for further processing and secretion. Because the binding site of BIP is located in the C_H1 domain, when a mutant HC lacks the C_H1 domain, it fails to associate with BIP and thus may be secreted as a free subunit in the circulation. However, C_H1 deletion seems necessary but not sufficient for deposition, and it is likely that the V_H also contributes to tissue deposition, ultrastructural aspects of the deposits, and ECM accumulation. Indeed, in HC disease, a lymphoproliferative disorder with free HC secretion without corresponding tissue deposition, the variable regions are found to be deleted partially or entirely, together with the C_H1 domain. In HCDD, the variable regions are present without major structural alteration, although in the two cases in which they were sequenced (8,22), they contained unusual amino acid substitutions that might change the physicochemical properties (e.g., charge, hydrophobicity). In addition, the structure of an HCDD HC (8) was strikingly similar to that reported in a case of amyloid HC amyloidosis (23), from which it differed essentially at the V domain level. It is worth noting that in most cases of HCDD, the circulating HC is associated with a \( \lambda \)-type LC. This bias may reflect a preferential association of the V_H with \( \lambda \) V_L domains.

Deposition Does Not Mean Pathogenicity

The finding by Solomon et al. (24) of unexpectedly frequent (14 of 40) deposition of human monoclonal LC along basement membranes in a mouse experimental model raises the question of the relationship between tissue precipitation and pathogenic effects. Human LC that were found deposited along basement membranes in mice were predominantly of the \( \lambda \) type (9 of 14), contrasting with the striking predominance of \( \kappa \) chains in MIDD (24). In addition, LC deposition similar in aspect to LCDD by immunofluorescence but with no or only scanty granular electron-dense deposits in the tubular basement membrane may occur in the absence of glomerular lesions and tubular basement membrane thickening (19,25). One patient (Aucouturier P, Droz D, personal data) had an important LC secretion and typical basement membrane deposits by immunofluorescence in the kidney, without histologic alteration, and with normal renal functions 2 yr after kidney biopsy. Thus, the propensity of a given LC to form deposits does not necessarily mean that it is pathogenic, and immunofluorescence staining should not be considered a sufficient criterion for pathologic diagnosis of MIDD. As shown by characteristic pathologic changes and experimental evidence, MIDD lesions are associated with local fibrosis.

LC-Induced Mesangial Fibrosis

Results of an in vitro study (26) suggest that pathogenic Ig chains may stimulate mesangial cells to secrete ECM components through growth factors, in particular transforming growth factor-\( \beta \) (TGF-\( \beta \)). LC-induced overproduction of collagen IV, laminin, fibronectin, and tenascin was shown to be maximal at 72 h of incubation with mesangial cells (27). Accumulation may be increased by a concomitant inhibition of collagenase IV, which also is mediated by TGF-\( \beta \). None of these effects was found with amyloid LC (27). One way to prevent the LC-induced fibrosis is to study the detailed mechanism of putative ligand-receptor interactions that may govern the ability of a given LC to stimulate the ECM synthesis. Other possibilities are to prevent the secretion of TGF-\( \beta \) or to interfere with the TGF-\( \beta \) signaling pathway.

Renal Pathology

Light Microscopy

Despite clinical manifestations that feature impairment of glomerular function in most cases, MIDD should not be considered a purely glomerular disease. In fact, tubular lesions may be more conspicuous than the glomerular damage. Tubular lesions are characterized by the deposition of a refractile, eosinophilic, periodic acid-Schiff (PAS)-positive, ribbon-like material along the tubular basement membrane (Figure 2A).

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Light microscopy of an LC nephropathy with predominant tubulointerstitial lesions. (A) Thickening of tubular basement membranes and diffuse interstitial fibrosis. (B) Strongly periodic acid-Schiff (PAS)-positive deposits delineating the spaces between myocytes in an interlobular artery. Magnifications: \( \times 125 \) in A (PAS); \( \times 312 \) in B (PAS).
The deposits predominate around the distal tubules, the loops of Henle, and, in some instances, the collecting ducts whose epithelium is flattened and atrophied. Typical myeloma casts are only occasionally seen in pure forms of MIDD (see below for association with myeloma cast nephropathy). In advanced stages, a marked interstitial fibrosis including refractile deposits frequently is associated with tubular lesions. Glomerular lesions are much more heterogeneous (28,29). Nodular glomerulosclerosis (NGS) is the most characteristic; it is found in 60 (30) to 100% (19) of patients with LCDD. Expansion of the mesangial ECM was observed in all cases of HCDD, with NGS in almost all of them. Mesangial nodules are composed of PAS-positive membrane-like material and often are accompanied by mild mesangial hypercellularity. The capillary loops stretch at the periphery of florid nodules and may undergo aneurysmal dilation. Bowman’s capsule may contain a material that is identical to that present in the center of the nodules. These lesions resemble nodular diabetic glomerulosclerosis, but some characteristics are distinctive: the distribution of the nodules is fairly regular in a given glomerulus, the nodules are poorly argyrophilic, and exudative lesions as “fibrin caps” and extensive hyalinosis of the effenter arterioles are not observed. In occasional cases with prominent endocapillary cellularity and mesangial interposition, the glomerular features mimic lobular glomerulonephritis. Milder forms of LCDD simply show an increase in mesangial matrix and sometimes in mesangial cells and a modest thickening of the basement membranes that are abnormally bright and rigid. Glomerular lesions may not even be detected by light microscopy but require ultrastructural examination. These lesions may represent early stages of glomerular disease or be induced by LC with a weak pathogenic potential. Their diagnosis would be unrecognized without the immunostaining results. Arteries, arterioles, and peritubular capillaries all may contain PAS-positive deposits in close contact with their basement membranes (Figure 2B). Deposits do not show the staining characteristics of amyloid, but they may be associated with Congo red–positive amyloid deposits in approximately 10% of patients (19).

**Immunofluorescence Microscopy**

A key step in the diagnosis of the various forms of MIDD is immunofluorescence examination of the kidney. All biopsy specimens show evidence of monoclonal LC (mostly k) and/or HC fixation along tubular basement membranes. This criterion is requested for the diagnosis of MIDD.

The tubular deposits stain strongly and predominate along the loops of Henle and the distal tubules, but they also often are detected along the proximal tubules. In contrast, the pattern of glomerular immunofluorescence displays marked heterogeneity. In patients with NGS, deposits of monoclonal Ig chains usually are found along the peripheral glomerular basement membranes and, to a lesser extent, in the nodules themselves. The staining in glomeruli typically is weaker than that observed along the tubular basement membranes. This may not be a function of the actual amount of deposited material, because several cases in which glomerular immunofluorescence was negative despite the presence of large amounts of granular glomerular deposits by electron microscopy have been reported (31). Local modifications of deposited LC thus might change their antigenicity (18). In patients without nodular lesion (Figure 3A), glomerular staining occurs mainly along the basement membrane, but it may involve the mesangium in some cases. A linear staining usually decorates Bowman’s capsule. Deposits frequently are found in vascular walls and interstitium.

In patients with HCDD, immunofluorescence with anti-LC polyclonal and monoclonal antibodies is negative despite typical NGS. Monotypic deposits of γ, α, or μ HC may be identified. All γ subclasses may be observed. Analysis of the kidney biopsy with monoclonal antibodies specific for the constant domains of the γ HC allowed identification of a deletion of the C_H 1 domain in all tested cases. In most cases of HCDD, except those with deposits of γ_4 that does not activate complement, complement components could be demonstrated in a granular or pseudolinear pattern.

The accessory proteins (serum amyloid P component, apolipoprotein E, and ubiquitin) that are associated with AL amyloidosis and other amyloidoses are not present in LCDD deposits.

The composition of glomerular matrix proteins has been examined comparatively in NGS associated with LCDD and diabetes mellitus (32). Nodules are made of normal ECM constituents (collagen type IV, laminin, fibronectin) that are produced in excess and stain weakly for the small proteoglycans, decorin and biglycan (33). In a series of 36 patients with LC-related renal diseases including AL amyloidosis, cast nephropathy, fibrillary glomerulopathy, and LCDD, TGF-β was detected only in glomeruli of the 3 patients with LCDD and nodular glomerular lesions (34). In the control series, it was found essentially in nodular diabetic glomerulosclerosis, which may suggest that distinct initial insults to the glomerular mesangium may trigger similar fibrogenetic pathways.

**Electron Microscopy**

The most characteristic ultrastructural feature is the presence of finely to coarsely granular electron-dense deposits along the outer (interstitial) aspect of the tubular basement membranes. In the glomerulus, they predominate in a subendothelial position along the glomerular basement membrane and are located mainly along and in the lamina rara interna. They also can be found in mesangial nodules, Bowman’s capsule, and the wall of small arteries between the myocytes. Nonamyloid fibrils have been reported in a few patients with LCDD or HCDD.

**Association with Myeloma Cast Nephropathy**

The association of monoclonal LC deposits, mostly along renal tubule membranes, with typical myeloma cast nephropathy is more frequent than reported initially (see Figure 3, B and C). It was found in 23 of 72 (32%) patients with nonamyloid monoclonal LC deposits in a French series (30) and in 11 of 34 (32%) patients with MIDD in a recent North American study (19). NGS is, however, infrequent (<10%), and some ribbon-like tubular basement membranes are seen in fewer than...
half of the patients (30). In addition, one third of the patients do not have granular-dense deposits by electron microscopy. The lack of ECM accumulation in most of these patients who present with acute renal failure in the setting of a true myeloma may be due to insufficient time for the development of fibrosis or to a weaker sclerogenic effect of the LC, if any. As discussed previously, the presence of LC deposits along the tubular basement membrane is not sufficient to make a diagnosis of MIDD.

Clinical Features of LCDD

The main clinical features of MIDD are renal and cardiac manifestations, as in AL amyloidosis. Data collected from the largest series as yet published (1,19,29,35–37) show an unexpectedly wide range of affected ages (35 to 80 yr) with a male gender preponderance. Mean age tends to be higher in patients with LCDD and myeloma cast nephropathy (67 yr) (19) than in those with pure MIDD (51 to 58 yr).

Renal Disease

Renal involvement is a constant feature of MIDD, and proteinuria (composed mostly of albumin) and renal failure often dominate the clinical presentation. In 23 to 53% of the patients, albuminuria is associated with nephrotic syndrome. However, in approximately 25% of them, it is less than 1 g/d, and these patients exhibit mainly a tubulointerstitial syndrome (Figure 2A). Albuminuria is not correlated with the existence of NGS, at least initially, and may occur in the absence of significant glomerular lesions by light microscopy. Hematuria is more frequent (29 to 67%) than one would expect for a nephropathy in which cell proliferation usually is modest, with a few exceptions. The prevalence of hypertension is variable but must be interpreted according to medical history.

The high prevalence (>90%), early appearance, and severity of renal failure are other salient features of MIDD. In most cases, renal function declines rapidly, which is a main reason for referral.

Figure 3. (A) Immunofluorescence of renal biopsy specimen from a \( \kappa \) LC nephropathy without nodular glomerulosclerosis. Bright staining is shown along tubular basement membranes, and heavy deposits are shown in an arteriolar wall. Glomerular staining involves Bowman’s capsule and capillary basement membranes as well as mildly increased mesangium. (B) In a patient who presented with overt myeloma and acute renal failure, direct immunofluorescence of renal biopsy specimen with the use of anti-\( \kappa \) antibody showed numerous myeloma casts and staining of most of the tubular basement membranes. (C) In the same patient, examination of a post mortem liver biopsy revealed \( \kappa \) deposits along sinusoids. (D) Renal biopsy from a patient with HC deposition disease. Direct immunofluorescence with fluorescein-conjugated anti-\( \gamma \) antibody shows bright staining of mesangial nodular areas and peripheral capillary walls but, in this case, no staining along basement membranes of the surrounding tubules. Magnification, \( \times 312 \).
Renal features of the 22 patients with HCDD basically are similar to those seen in LCDD and LHCDD (see below).

**Extrarenal Manifestations**

MIDD is a systemic disease, but visceral LC deposits may be totally asymptomatic and found only at autopsy. Liver and cardiac involvements are the most common (29).

Liver deposits were constant in patients whose liver was examined (38) (Figure 3C). They are discrete, confined to sinusoids and basement membranes of biliary ductules without associated parenchymal lesions, or massive with marked dilation and multiple ruptures of sinusoids resembling peliosis. Hepatomegaly with mild alterations of liver function tests are the most usual symptoms, but several patients develop hepatic insufficiency and portal hypertension, and some of them die of hepatic failure (29).

Cardiac manifestations have been noted in as many as 80% of the reported cases of LCDD, but they must be interpreted with caution because of other age-dependent potential causes of heart disease. Arrhythmias, conduction disturbances, and congestive heart failure are seen. Echocardiography and catheterization may reveal diastolic dysfunction and a reduction in myocardial compliance similar to that seen in cardiac amyloid. As in the kidney and the liver, immunofluorescence showed monotypic LC deposits in the vascular walls and perivascular areas of the heart in all autopsy cases (16).

Deposits also may occur along the nerve fibers and in the choroid plexus, as well as in the lymph nodes, bone marrow, spleen, pancreas, thyroid gland, submandibular glands, adrenal glands, gastrointestinal tract, abdominal vessels, lungs, and skin. They may be responsible for peripheral neuropathy (20% of the reported cases), gastrointestinal disturbances, pulmonary nodules, amyloid-like arthropathy, and sicca syndrome.

**Hematologic Disease**

The most common underlying disease in MIDD is myeloma, which accounts for 40 to 50% of pure MIDD (1,19,29,35–37) and >90% of LC deposits associated with myeloma cast nephropathy. MIDD and AL amyloidosis are found at postmortem examination in 5 and 10% of myeloma patients, respectively (39). MIDD, like AL amyloidosis, often is the presenting disease that leads to the discovery of myeloma at an early stage. In some patients who first presented with “common” myeloma and with normal-sized monoclonal Ig without kidney disease, LCDD occurred when the disease relapsed after chemotherapy, together with Ig structural abnormalities (7,16). Because melphalan was shown to induce Ig gene mutations, the disease in these patients might result from the emergence of a variant clone induced by the alkylating agent. Apart from myeloma, MIDD may complicate Waldenström’s macroglobulinemia and chronic lymphocytic leukemia in rare cases (17). It often occurs in the absence of a detectable malignant process, even after prolonged (>10 yr) follow-up. In such “primary” forms, a monoclonal bone marrow plasma cell population can be documented easily by immunofluorescence examination.

**Diagnostic Investigation**

The diagnosis of MIDD must be suspected in any patient who has nephrotic syndrome or rapidly progressive tubulointerstitial nephritis or who has echocardiographic findings that indicate diastolic dysfunction and a monoclonal Ig component in the serum and/or the urine. The same combination also is seen in AL amyloidosis, but the latter more often is associated with the λ LC isotype. Because sensitive techniques, including immunofixation, fail to identify a monoclonal Ig component in 15 to 30% of patients, renal biopsy plays an essential role in the diagnosis of MIDD and of the associated dysproteinemia.

The definitive diagnosis is made by the immunohistologic analysis of tissue from an affected organ, in most cases the kidney, with the use of a panel of Ig chain–specific antibodies, including anti-κ and anti-λ LC antibodies to stain the noncongophilic deposits. When the biopsy stains for a single HC isotype and does not stain for LC isotypes, the diagnosis of HCDD should be suspected (see below).

The diagnosis of plasma cell dyscrasia relies on bone marrow aspiration and bone marrow biopsy with cell morphologic evaluation and, if necessary, immunophenotyping with anti-κ and anti-λ antisera to demonstrate monoclonality. Diagnostic criteria for a multiple myeloma are present in no more than 50% of the patients with LCDD.

**Variants of LCDD: LHCDD and HCDD**

A monotypic HC is associated with the monotypic LC in approximately 10% of patients with LCDD. Whether HC and LC precipitate as independent subunits or as a whole Ig molecule remains to be established. In one case, we found different patterns of kidney deposition of the HC and LC (Rose C, unpublished observation). Anomalies of the HC structure suggesting deletion were demonstrated in LHCDD (7). Clinical presentation and pathologic data in patients with LHCDD are similar to those in LCDD.

The first patients with HCDD were reported in 1993 (8). Twenty-two cases have been described so far (19 and reviewed in reference 20). The clinical and pathologic features of HCDD basically are the same as in LCDD, although several differences can be noted. First, lesions of NGS are constant in patients with HCDD, whereas only a faint staining of tubular basement membranes was seen in some patients (Figure 3D). Second, extrarenal deposits are less frequent in these patients than in those with LCDD. They have been reported in heart, in synovial tissue, in skin, in striated muscles, in pancreas, around thyroid follicles, and in Disse spaces of the liver (8 and reviewed in reference 20). Third, signs of complement activation with renal complement deposition are present in most patients with γκ or γλ HCDD (19).

In some patients with HCDD, a monoclonal component cannot be detected in serum and urine (8). In other patients, a monoclonal IgGκ can be found in serum, but no deletion is found in the HC (9). Identification of the nephritogenic deleted HC that circulates in low amounts then requires serum fractionation followed by Western blotting (9) (Figure 4). This finding suggests that serum fractionation also should be performed in patients with LCDD in whom usual immunochemical methods have failed to detect a circulating monoclonal component.
Outcome and Treatment

The outcome of MIDD remains uncertain, mainly because extrarenal deposits of LC can be totally asymptomatic or cause severe organ damage that leads to death. Survival from onset of symptoms varies from 1 mo to 10 yr, whereas by comparison, the prognosis of a related disease, AL amyloidosis, is much more homogeneous with a median survival time of 18 mo under chemotherapy (40). Although renal prognosis is poor, patient survival can be considerable with 70 and 37% 5-yr patient survival and renal survival, respectively (36). The only predictor of renal patient survival seems to be the initial serum creatinine at the time of biopsy, whereas the presence of multiple myeloma does not seem to influence renal or patient survival (19). Outcomes in terms of renal and patient survival are significantly better in patients with pure MIDD, compared to patients with severe visceral involvement.

As in AL amyloidosis, treatment should be aimed at reducing Ig production. Chemotherapy is logical in patients with MIDD and myeloma. It is controversial in the absence of overt malignancy given the uncertain outcome of LCDD and the absence of reliable follow-up criteria, especially in patients without detectable M component. However, it has become general practice to treat patients with steroids plus melphalan or a cytotoxic agent, irrespective of the accompanying hematologic disease.

Whether appropriate treatment can result in sustained remission has long remained unclear. Clearance of the LC deposits has been demonstrated unequivocally in some patients after intensive chemotherapy with synergistic bone marrow transplantation or blood stem cell autografting (41,42). Disappearance of nodular mesangial lesions and LC deposits also was reported after long-term chemotherapy (43). These observations are of paramount importance: they demonstrate that fibrotic nodular glomerular lesions are reversible, and they argue for intensive chemotherapy in patients with severe visceral involvement.

Kidney transplantation has been performed in a few patients with MIDD and end-stage renal failure. Recurrence of the disease usually is observed. Therefore, intensive chemotherapy should be performed before kidney transplantation.

In conclusion, MIDD is a rare systemic disease that is characterized by severe renal failure as a result of the deposition of a monoclonal LC and/or HC of Ig. Glomerular lesions are more homogeneous than in diabetic nephropathy that MIDD may serve as a model for the understanding of this plague of the third millennium. MIDD indeed is the only sclerotic glomerular disease in which the offending molecule is defined perfectly. As in AL amyloidosis, controlled trials are required to define the best chemotherapy combination according to clinical presentation and severity of renal failure.

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References


