Immunoglobulin Light (Heavy)-Chain Deposition Disease: From Molecular Medicine to Pathophysiology-Driven Therapy

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Light-, light- and heavy-, and heavy-chain deposition diseases belong to a family of diseases that include light-chain (AL)-amyloid, nonamyloid fibrillary and immunotactoid glomerulonephritis, and cryoglobulinemic glomerulonephritis, in which monoclonal Ig or their subunits become deposited in kidney. In clinical and pathologic terms, light-, light- and heavy-, and heavy-chain deposition diseases essentially are similar and are characterized by prominent renal involvement with severe renal failure; extrarenal manifestations; diabetes-like nodular glomerulosclerosis; marked thickening of tubular basement membranes; and monotypic deposits of light chain, mostly κ, and/or heavy chain that feature a nonorganized granular, electron-dense appearance by electron microscopy. The most common cause is myeloma. Recent progress has been made in the understanding of the molecular pathomechanisms of Ig-chain deposition and extracellular matrix accumulation, which opens up new therapeutic avenues in addition to eradication of the Ig-secreting plasma cell clone. Because these diseases represent a model of glomerular and interstitial fibrosis that is induced by a single molecule species, a better understanding of their pathomechanisms may help to unravel the pathophysiology of kidney fibrosis and renal disease progression.


Since the first description of Ig amyloidosis by Glenner et al. in 1971 (1), the spectrum of glomerular diseases with deposition or precipitation of monoclonal Ig components has expanded dramatically. These diseases can be classified into two categories on the basis of electron microscopy (2). 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. The second category of diseases is characterized by nonorganized electron-dense granular deposits that are localized along basement membranes in most tissues, especially in the glomerulus and the renal tubule. It was known from the late 1950s that nonamyloidotic forms of glomerular disease that resemble the lesion of diabetic glomerulosclerosis could occur in multiple myeloma. The presence of monoclonal light chains (LC) in these lesions first was recognized in 1973 by Antonovych et al. (3) and confirmed by Randall et al. (4), who published in 1976 the first description of light-chain deposition disease (LCDD). Monoclonal heavy chains (HC) were found together with LC in the tissue deposits from some patients, and the term light- and heavy-chain deposition disease (LHCD) was proposed (5). Deposits that contain monoclonal HC only first were observed in 1993 in patients who were affected with otherwise typical Randall’s disease (HC deposition disease [HCDD]) (6), and two series of similar patients were published later (7,8).

In clinical and pathologic terms, LCDD, LHCD, and HCDD essentially are similar and now are described under the general term of monoclonal Ig deposition disease (MIDD). They differ from amyloidosis in that the deposits lack affinity for Congo red and do not have a fibrillar organization. The distinction also relates to different pathophysiology of amyloid, which implicates one-dimensional elongation of a pseudocrystalline structure, and of MIDD, which would rather involve a one-step precipitation of Ig chains.

Epidemiology

LCDD is found in 5% of patients with myeloma at autopsy, whereas the prevalence of light-chain (AL)-amyloidosis is approximately 11% (9). Twenty-three cases of MIDD (without myeloma cast nephropathy), including 12 LCDD, five LHCD, and six HCDD, were identified among the 7241 (0.33%) biopsies that were processed at New York-Presbyterian Hospital from 1982 to February 2000 (8). LCDD and HCDD may occur in a wide range of ages (26 to 94 yr) with a male preponderance (Table 1).

Pathogenesis

MIDD is characterized by kidney deposition of monoclonal Ig subunits, but at variance with amyloidosis, deposition in-
duces a dramatic accumulation of extracellular matrix (ECM) that is responsible for glomerular and tubular basement membrane thickening, nodular glomerulosclerosis, and interstitial fibrosis. That LC deposition involves unusual LC properties is supported by the absence of a detectable monocalonal component in the serum and urine in 10 to 20% of patients with LCDD, the recurrence of the disease in the transplanted kidney, and the biosynthesis of abnormal LC by bone marrow plasma cells (5,10). However, LC deposition does not mean pathogenicity, because after injection into mice, one third of LC from patients with myeloma or AL-amyloidosis became deposited in basement membranes (11). Therefore, singular properties of LC most likely are required for completion of the pathogenetic process that leads to kidney fibrosis.

**Structure and Glycosylation of LC in LCDD**

In LCDD, isotype restriction is significant: \( \kappa \) chains occur in approximately 80% of cases, which contrasts with the increased \( \lambda \) to \( \kappa \) ratio that is seen in amyloidosis, and the rare V\(_{\text{LIV}}\) variability subgroup may be overrepresented (12) (Figure 1a). This subgroup features a longer complementarity-determining region 1 (CDR1) loop (which is part of the antigen binding site) that contains several unusual hydrophobic residues. The role of the LC variable region V\(_{\text{L}}\) in LC deposition is suggested by the fact that amino acid changes in V\(_{\text{L}}\) were sufficient to promote tissue deposition in mice that expressed a human LCDD V\(_{\text{LIV}}\) chain (13).

The first complete primary structure of an LC in LCDD was determined by Cogné et al. in 1991 (14). The 30-kD \( \kappa \) chain that was found in the kidney presumably was identical to that secreted by the malignant plasma cells because they shared the same apparent molecular mass and 13–amino acid N-terminal sequence. It was encoded by a normal-sized mRNA and was N-glycosylated. The C region was entirely normal, and the V region belonged to the V\(_{\text{LIV}}\) subgroup. Eight mutations were observed, including replacement of Pro95 (considered as essential for canonical conformations of the CDR3 loop). Replacement of Asp70 by Asn determined an N-glycosylation site. The primary structures of a few additional LCDD precursors were analyzed at the complementary DNA (15,16) and protein levels (17). Most peculiarities were clustered in peptide loops that corresponded to the CDR, suggesting that a first step of the pathogenesis could be an LC tropism for extracellular components that behave as antigen-like structures. Unusual hydrophobic residues were found at positions where they could either strongly modify the LC conformation, potentially leading to LC aggregation, or be involved in interactions with other hydrophobic molecules in the intracellular space (18) (Figure 1b).

When pathogenic LC could not be detected in the serum and urine, they were N-glycosylated in all tested cases (12,19). *In vitro* biosynthetic labeling experiments on short-term plasma cell cultures showed that LC that were absent in the urine actually were secreted by the bone marrow plasma cells (5,10,14). Together with the presence of hydrophobic residues, glycosylation might increase the LC propensity to precipitate in tissue and displace the equilibrium from soluble toward deposited amorphous forms.

As in AL-amyloidosis, extrinsic conditions also may contribute to aggregation of the LC. The same LC can form granular aggregates or amyloid fibrils, depending on the environment, and different partially folded intermediates of this protein may be responsible for amorphous or fibrillar aggregation pathways (20).

**HCDD: A Disease Featured by HC Deletions**

A deletion of the first constant domain C\(_{\text{H1}}\)1 was found in the deposited or circulating HC in the 11 patients with \( \gamma \)-HC deposition disease, where it was searched for (6–8,21,22). It also was suggested in a patient with \( \alpha \) HCDD (23). A larger deletion that also included the C\(_{\text{H1}}\)1 domain, the hinge, and the C\(_{\text{H2}}\)2 domain was found in one case (6). In the blood, the deleted HC could be associated with an LC, mostly of the \( \lambda \) isotype, or circulated in small amounts as a free unassembled subunit (7).

The C\(_{\text{H1}}\)1 deletion is required for secretion of free HC, which are cleared rapidly from the circulation by organ deposition (2). Deletion of the C\(_{\text{H1}}\)1 also is found in HC disease, a lymphoproliferative disorder with free HC secretion without renal tissue.

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**Table 1. Comparison of clinical manifestations, renal lesions, and hematologic features in patients with MIDD**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LCDD/LHCDD</th>
<th>HCDD</th>
</tr>
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<tbody>
<tr>
<td>Male/female ratio</td>
<td>1.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57 (28 to 94)</td>
<td>57 (26 to 79)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>53</td>
<td>90</td>
</tr>
<tr>
<td>Renal failure (serum creatinine ≥130 μmol/L; %)</td>
<td>93</td>
<td>83</td>
</tr>
<tr>
<td>Nephrotic syndromeb (%)</td>
<td>36</td>
<td>46</td>
</tr>
<tr>
<td>Hematuria (%)</td>
<td>45</td>
<td>89</td>
</tr>
<tr>
<td>Nodular glomerulosclerosis (%)</td>
<td>31 to 100</td>
<td>96</td>
</tr>
<tr>
<td>Multiple myeloma (%)</td>
<td>53</td>
<td>24</td>
</tr>
<tr>
<td>M component (blood or urine) (%)</td>
<td>88</td>
<td>58c</td>
</tr>
</tbody>
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a From Ronco et al. (46). HCDD, heavy-chain deposition disease; LCDD, light-chain deposition disease; LCHDD light- and heavy-chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease.

b Proteinuria ≥3 g/d.

c Including two cases with only free \( \kappa \) chain.
deposition, and in heavy-chain (AH)-amyloidosis in which deposits have a fibrillar organization. In HC disease, however, the variable domain also is partially or completely deleted, which suggests that the VH domain is involved in tissue precipitation.

Sequence analysis of two HCDD proteins did show unusual amino acid substitutions in the VH, which might change their physicochemical properties, including charge and hydrophobicity (24).

Pathophysiology of ECM Accumulation
A striking feature of MIDD is the dramatic accumulation of ECM, whose pathogenesis is beginning to be understood. Nodules are made of normal constituents (collagen type IV, laminin, fibronectin, and tenascin) (25,26) and stain weakly for the small proteoglycans decorin and biglycan (27). Tenascin is an ECM protein that is a component of the mesangium in normal and, most important, in pathologic conditions (28). Tenascin was shown to accumulate in the center of mesangial nodules in patients with LCDD and nodular glomerulosclerosis (26). Tenascin production by mesangial cells is enhanced in the in vitro model (29) as well as in patients with LCDD. Deposition of tenascin might be involved in the perpetuation and irreversibility of the glomerular lesion in LCDD.

A role for TGF-β is supported by its strong expression in glomeruli of patients with LCDD and by in vitro experiments using cultured mesangial cells (30). Incubation of mesangial cells with LC from patients with LCDD induced cell changes, activation of PDGF-β and its receptor, production of monocyte chemoattractant protein-1, and increased expression of Ki-67, a proliferation marker, whereas tubulopathic LC had no effect (31). The resulting phenotype is close to myofibroblastic phenotype, including activation of ECM synthesis and decreased matrix metalloproteinase production and activity (26,32) (Figure 2). In contrast, mesangial cells that are incubated with LC from patients with AL-amyloidosis undergo a macrophage-like transformation, with increased matrix metalloproteinase activity and decreased ECM production (32). Those divergent phenotypic transformations may be related to distinct cellular trafficking of LCDD and AL-amyloid LC after binding to a yet unidentified, common caveola-associated receptor (33). AL-amyloid LC are delivered to the mature lysosomal compartment, whereas amyloid formation occurs, whereas LCDD LC do not show significant internalization (33). Whether these events...
occur in vivo remains to be established. Understanding the signaling pathways that are triggered by LC binding to mesangial cells may contribute substantially to our knowledge on the mechanisms of glomerulosclerosis.

**Clinical Manifestations**

MIDD is a systemic disease with Ig-chain deposition in a variety of organs, leading to various clinical manifestations (2), but visceral Ig-chain deposits may be totally asymptomatic and found only at autopsy.

**Renal Manifestations**

Renal involvement is a constant feature of MIDD, and renal symptoms, mostly proteinuria and renal failure, often dominate the clinical presentation (Table 1) (5,8,34–36). In 18 to 53% of patients with LCDD, albuminuria is associated with the nephrotic syndrome. However, in approximately one quarter, it is <1 g/d, and these patients exhibit mainly a tubulointerstitial syndrome. Albuminuria is not correlated with the existence of nodular glomerulosclerosis and may occur in the absence of significant glomerular lesions as detected by light microscopy. Hematuria is more frequent than one would expect for a nephropathy in which cell proliferation usually is modest.

The high prevalence, early appearance, and severity of renal failure are other salient features of LCDD (2,4,8,34,37). In most cases, renal function declines rapidly, which is a main reason for referral. Renal failure occurs with comparable frequency in patients with either low or heavy protein excretion and may present in the form of an acute tubulointerstitial nephritis (38) or a rapidly progressive glomerulonephritis, respectively. The prevalence of hypertension is variable, but it must be interpreted according to associated medical history.

Renal features of patients with HCDD are basically similar to those that are seen in LCDD and LHCD (Table 1), with a higher prevalence of hypertension, glomerulosclerosis, and microhematuria. Deposition of certain HC subclasses, especially IgG3, frequently features classical pathway activation and hypocomplementemia (22).

**Extrarenal Manifestations**

Liver and cardiac involvement occur in approximately one quarter of patients with LCDD and LHCD (35). Liver deposits are constant. They either are discrete and confined to the sinusoids and basement membranes of biliary ductules without associated parenchymal lesions or are 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 patients also may develop life-threatening hepatic insufficiency and portal hypertension (19).

Cardiac involvement may be responsible for cardiomegaly and severe heart failure. Arrhythmias, conduction disturbances, and congestive heart failure are seen. Echocardiography and catheterization may reveal diastolic dysfunction and reduction in myocardial compliance similar to that found in cardiac amyloid. As in the kidney and liver, monotypic LC deposits in the vascular walls and perivascular areas of the heart were observed in all autopsy cases (19).

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 (2). They may be responsible for peripheral neuropathy (20% of the reported cases), gastrointestinal disturbances, pulmonary nodules, amyloid-like arthropathy, and sicca syndrome. In some patients, nonamyloidotic localized nodules, termed “aggregomas,” develop in the lung or as cervical mass without systemic LCDD (39–41).

Extrarenal deposits are less common in patients with HCDD. They have been reported in the heart (21), synovial tissue (21,42), skin (43), striated muscles (43), and pancreas (6); around the thyroid follicles (6); and in Disse’s spaces (lymphatic channels) in the liver.

**Hematologic Findings**

Myeloma is diagnosed in approximately 50% of patients with LCDD or LHCD and in approximately 25% of those with HCDD. MIDD, like AL-amyloidosis, often is the presenting disease that leads to the discovery of myeloma at an early stage. In some patients who presented with “common” myeloma and normal-sized monoclonal Ig without kidney involvement, LCDD occurred when the disease relapsed after chemotherapy, together with Ig structural abnormalities (19). Because melphalan may induce Ig gene mutations, the disease in these patients might result from the emergence of a variant clone caused by the alkylating agent. MIDD occasionally may complicate Waldenström’s macroglobulinemia, chronic lymphocytic leukemia, and nodal marginal-zone lymphoma (44). It often occurs in the absence of a detectable malignant process, even after prolonged (>10 yr) follow-up. A monoclonal bone marrow plasma cell population then is easily detectable by immunofluorescence examination.

**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 outer part of the tubular basement membrane (Figure 3). 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 seen only occasionally in pure forms of MIDD. In advanced stages, a marked interstitial fibrosis that includes refractile deposits frequently is associated with tubular lesions.

Glomerular lesions are much more heterogeneous (2). Nodular glomerulosclerosis is the most characteristic (Figure 3); it is found in 30 to 100% of patients with LCDD (2,8). Expansion of the mesangial matrix was observed in all cases of HCDD, with
nodular glomerulosclerosis in almost all of them (7). Mesangial nodules are composed of PAS-positive membrane-like material. These lesions resemble diabetic nodular glomerulosclerosis, but some characteristics are distinctive: The distribution of the nodules is fairly regular in a given glomerulus, the nodules often are poorly argyrophilic, and exudative lesions as “fibrin caps” and extensive hyalinosis of the efferent arterioles are not observed. Milder forms of LCDD simply show an increase in mesangial matrix and cells and a modest thickening of the basement membranes. Glomerular lesions may not 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. 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 (8).

Immunofluorescence

A key step in the diagnosis of the various forms of MIDD is immunofluorescence examination of the kidney. All renal biopsies should be stained routinely for κ and λ LC. All biopsy specimens from patients with LCDD show evidence of monotypic LC (mostly κ) fixation along tubular basement membranes (Figure 3). This criterion is required for the diagnosis of LCDD.

The tubular deposits stain strongly (Figure 3) 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 nodular glomerulosclerosis, deposits of monotypic Ig chains usually are found along the peripheral glomerular basement membranes (GBM) and, to a lesser extent, in the nodules themselves (Figure 3). The staining in glomeruli typically is weaker than that observed along the tubular basement membranes. Local modifications of deposited LC might change their antigenicity (19). In patients without nodular lesions, glomerular staining occurs mainly along the basement membrane. 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 antibodies is negative despite typical nodular glomerulosclerosis. Monotypic deposits of γ, α, or μ HC may be identified. Any γ subclass may be observed. Analysis of the kidney biopsy with mAb that are specific for the constant domains of the γ HC allowed identification of a deletion of the C1 domain in all tested cases (2,7,8). In most cases of HCDD, especially when a γ1 or γ3 chain is involved, complement components including C1 could be demonstrated in a granular or pseudolinear pattern. Complement deposits often were associated with decrease of serum complement (7,8,22,45).

Electron Microscopy

The most characteristic ultrastructural feature is the presence of finely or coarsely granular electron-dense deposits that de-
lineate the outer aspect of the tubular basement membranes. They appear to be in contact with a well-preserved basal lamina. The deposits usually are large and may protrude into the adjacent part of the interstitium.

In glomeruli, a nonfibrillar, electron-dense material is seen in the mesangial nodules and along the GBM. The mesangial material usually is finely granular (Figure 4). The deposits along the GBM appear as a prominent but thin, continuous band delineating the endothelial aspect of the basement membrane (Figure 4). In rare cases, the deposits invade the lamina densa. Deposits also can be found in Bowman’s capsules and in the wall of small arteries between the myocytes (2). In some cases, conclusive evidence of monotypic LC deposition can be obtained by using immunoelectron microscopy (38).

**Diagnosis**

The diagnosis of MIDD must be suspected in any patient with the nephrotic syndrome or rapidly progressive tubulointerstitial nephritis or with echocardiographic findings indicating diastolic dysfunction and the presence of a monoclonal Ig component in the serum and/or the urine (Figure 5). The same combination also is seen in AL-amyloidosis, but this more often is associated with the λ LC isotype. Because sensitive techniques including immunofixation fail to identify a monoclonal Ig component in 10 to 20% of patients with LCDD/LHCDD and approximately 40% of patients with HCDD (46), 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, using a panel of Ig chain-specific antibodies, including anti-κ and anti-λ LC antibodies to stain the non-Congophilic deposits. When the biopsy stains for a single HC isotype and does not stain for LC isotypes, the diagnosis of HCDD should be suspected. The diagnosis of the plasma cell dyscrasia relies on bone marrow aspiration and biopsy with cell morphologic evaluation and, if necessary, immunophenotyping with anti-κ and anti-λ antisera to demonstrate monoclonality.

**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. In the largest series (34), 57% of the patients reached uremia and 59% died during follow-up (mean 27.5 mo), and patient survival was only 66% at 1 yr and 31% at 8 yr, although 86% of the patients received chemotherapy. The only variables that were independently associated with renal survival were age and degree of renal insufficiency at presentation (34) or the time of renal biopsy (8). Variables that were independently associated with a worse patient survival were age, initial creatinine, associated multiple myeloma, and extrarenal LC deposition (8,34). Survival of the uremic patients who were treated with dialysis was not different from that of the patients who did not reach uremia.

As in AL-amyloidosis, treatment should be aimed at reducing Ig production. Clearance of the LC deposits has been demonstrated unequivocally in a few patients after intensive chemotherapy with syngeneic bone marrow transplantation or blood stem cell autografting (47,48). Disappearance of nodular mesangial lesions and LC deposits also was reported after long-term chemotherapy (49). These observations demonstrate that fibrotic nodular glomerular lesions are reversible, and they argue for intensive chemotherapy in patients with severe visceral involvement.

In a recent retrospective study of 11 patients (<65 yr) who had L(H)CDD and were treated by high-dosage therapy with the support of autologous blood stem cell transplantation, no treatment-related death occurred (50). A decrease in the monoclonal Ig level was observed in eight patients, with complete disappearance from serum and urine in six cases. Improvement in manifestations related to deposits was observed in six patients, and histologic regression was documented in cardiac, hepatic, and skin biopsies. No manifestation related to deposits occurred or recurred in any patient. Reversal of dialysis dependence and sustained improvement in renal function also was
Renal Diseases Associated with MIDD

Myeloma Cast Nephropathy

The association of MIDD with typical myeloma cast nephropathy is more frequent than reported initially. It was found in 32% of patients with MIDD (8). Nodular glomerulosclerosis, however, is infrequent (<10%), and one third of the patients do not have granular-dense deposits by electron microscopy. The lack of matrix accumulation may relate to insufficient time for the development of fibrosis or to a weaker sclerogenic effect of the LC, if any (2).

AL-Amyloidosis

Amyloid deposits are found in one or more organs in approximately 7% of patients with LCDD (54). Although this association may result from peculiar LC that are endowed with intrinsic properties that make them prone to form both fibrillar and nonfibrillar deposits, depending on the environment (20), one cannot exclude the possibility that the coexisting diseases are induced by different variant clones.

Conclusion

MIDD is a rare systemic disease that is characterized by severe renal failure as a result of the deposition of a monotypic LC and/or HC of Ig. Glomerular lesions are so similar to diabetic nephropathy that MIDD may serve as a model for the understanding of this common disease. 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, and new therapeutic perspectives will be derived from a better understanding of the pathophysiology.

References

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