Onco-Nephrology: Glomerular Diseases with Cancer

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Summary
Glomerular diseases occurring in the course of malignancies remain rare. Diverse glomerular lesions can be observed in a variety of neoplasms and involve different pathophysiologic links between the glomerulopathy and the cancer. The pathophysiology of solid tumor–associated glomerulopathies remains obscure, whereas in hematologic malignancy–induced paraneoplastic glomerulopathies, a molecular link can usually be demonstrated. The aim of this review is to provide an update on glomerular diseases associated with carcinoma and hematologic malignancies, covering epidemiology, pathophysiology, clinical presentation, and therapy. Special emphasis will be placed on the potential usefulness of novel biomarkers, such as antiphospholipase A2 receptor antibodies, for the diagnosis of membranous nephropathy, and on new associations and recent entities, including (proliferative) GN with nonorganized monoclonal immunoglobulin deposits and myeloproliferative neoplasm–related glomerulopathy.


Introduction
The term paraneoplastic syndrome refers to clinical manifestations that are not directly related to tumor burden, invasion, or metastasis but are caused by the secretion of tumor cell products, such as hormones, growth factors, cytokines, and tumor antigens. The concept of paraneoplastic glomerulopathy was introduced by Galloway in 1922. Since then, the spectrum of paraneoplastic glomerulopathies has markedly expanded with the description of glomerular complications of hematologic malignancies. The relationship between malignancy and glomerular disease is better understood, allowing a more precise diagnostic approach and the description of new entities.

Epidemiology
The prevalence of renal involvement in patients with cancer has been analyzed in autopsy and clinical series. Data from autopsy series are conflicting because of technical limits to postmortem study. In clinical series, the prevalence (range, 7%–34%) is overestimated because the threshold of proteinuria was low and hematuria was detected by qualitative dipstick tests only (1,2).

The prevalence of cancer in patients with glomerulopathy is easier to establish. The first study, published by Lee et al., found that 11% of patients with the nephrotic syndrome had carcinoma (3). Analysis of the Danish Kidney Biopsy Registry, which included all biopsies performed in Denmark since 1985, showed that the risk for cancer at 1 year and 1–4 years after the diagnosis of glomerulopathy was increased by 2.4- and 3.5-fold, respectively, compared with risk in the general population (4). However, this result was not confirmed at 5 years or thereafter. The Tromso study described an association between albuminuria and cancer, with an increased risk for bladder and lung cancers (8.3- and 5.4-fold, respectively) in patients with an albumin-to-creatinine ratio in the highest quintile (5). Nevertheless, the relationship between glomerular disease and cancer can at times be misleading because of potential detection bias (e.g., in the case of membranous nephropathy, in which patients are likely to be more aggressively screened for cancer); the demographic characteristics of the population (e.g., membranous nephropathy and cancer tend to occur more often in the elderly); and the use of alkylating agents to treat glomerular disease, which can itself lead to subsequent malignancies.

Carcinoma-Associated Paraneoplastic Glomerulopathies

Membranous Nephropathy
Membranous nephropathy (MN) is a rare disease, whereas cancer is common. A secondary cause, such as systemic lupus erythematosus, hepatitis B, or other chronic infections, and various drugs can be found in approximately 20% of cases; the remaining cases are considered idiopathic or primary MN (6). The association between MN and cancer was first reported in 1966 (3). Since then, several case series suggested a strong link and emphasized the importance of an extensive screening for malignancy in patients diagnosed with MN without evident secondary cause (7,8). However, other authors believe that this association has been overemphasized (9). It is indeed intriguing that subepithelial deposits were not found, or were noted very infrequently, in autopsy series of patients with cancer (10).

The prevalence of cancer in patients with MN is estimated at 6%–22% (11). Malignancy is usually found within 12 months of the diagnosis of MN, and most
(80%) cases are discovered before or at the time of the renal diagnosis (7,12). Compared with age- and sex-adjusted general population, the standardized incidence ratio of cancer in patients with MN is 2.25; the annual incidence continues to increase for more than 5 years after the histologic diagnosis of nephropathy (13). The malignancies most frequently associated with MN are solid tumors, including lung, gastrointestinal, and prostate carcinomas (8,10,11,13). Not surprisingly, age and heavy smoking increase the likelihood of malignancy in MN patients. Patients with MN plus malignancy have a poorer prognosis than those without cancer (13).

The diagnosis of paraneoplastic glomerulopathy should rely on three strong criteria (11). First, a remission occurs after complete removal of the tumor by surgery, chemotherapy, or other treatments. Second, a renal relapse accompanies recurrence of the neoplasia. Third, a pathophysiologic link is established between cancer and MN, including the detection of tumor antigens (such as carcinoembryonic antigen and prostate-specific antigen) and antitumor antibodies within subepithelial immune deposits (9,11). However, their presence does not mean that they are causative because they can be passively deposited as a result of increased glomerular permeability to proteins. Four mechanisms recently reviewed by Beck (14) can be involved in malignancy-associated MN; however, they are not yet elucidated, in part because of the lack of a reliable experimental model (Figure 1).

Several advances have recently been made in MN pathophysiology, allowing a more precise distinction between idiopathic and malignancy-associated MN. In 2009, the transmembrane glycoprotein M-type phospholipase A2 receptor (PLA2R1) was identified as the major target podocyte antigen involved in the majority of adult idiopathic MN cases (15). The sensitivity and specificity of detection of anti-PLA2R1 antibody by immunoblot or immunofluorescence assay in idiopathic MN are about 70% and 90%, respectively, whereas a very low prevalence of these antibodies is observed in “secondary MN,” for which coincidental occurrence of idiopathic MN with the “associated” disease cannot be excluded (14–19). For instance, Qin et al. described few patients (3 of 10) having positivity for anti-PLA2R1 antibodies and MN associated with solid tumors, but all three patients showed persistence or relapse of proteinuria despite resection of the tumor; this finding suggests that the two diseases were not causally related (19). In idiopathic MN, IgG4 is the predominant subclass of anti-PLA2R1 antibodies showing co-localization with the PLA2R1 antigen within the subepithelial immune deposits (15), whereas in malignancy-associated MN, IgG1 and IgG2 are the prevailing subclasses (20). The absence of glomerular IgG4 deposition at an early stage could thus be an independent predictor for cancer occurrence (21). Sensitivity and specificity of the absence of IgG4 are 88% and 86%, respectively (21). Moreover, the presence of more than eight inflammatory cells infiltrating the glomeruli seems to strongly increase the likelihood of malignancy in patients with MN (sensitivity of 92% and specificity of 75%; Figure 2) (8).

These new findings will have a strong effect on the care of patients with a diagnosis of MN, who should benefit from the detection of circulating anti-PLA2R1 antibody and the study of IgG subclasses and inflammatory cells (Figure 3).

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**Figure 1.** Mechanisms by which solid tumors and membranous nephropathy (MN) may be linked. MN is defined by subepithelial deposits that form in the glomerular basement membrane (GBM) beneath the foot processes of the glomerular visceral epithelial cell, or podocyte. Antibodies may be generated against an antigen identical to, or bearing an epitope similar to, an endogenous podocyte antigen, thereby leading to *in situ* immune complex formation (A). Alternatively, shed tumor antigens may form circulating immune complexes that become trapped in the capillary wall (B). Complexes may initially form in a subendothelial location, dissociate, and reform in a subepithelial position. Tumor antigens also may, on the basis of size and charge, become planted in a subepithelial location, where they react with circulating antibodies at a later stage (C). Finally, extrinsic processes, such as infection with an oncogenic virus or altered immune function (D), potentially could cause both malignancy and MN. From reference 14, with permission.
Search for malignancy is warranted in older patients with newly diagnosed MN once other secondary causes have been excluded, especially if there is no anti-PLA2R1 antibody and a majority of IgG1 and IgG2 deposits. In addition to a search for personal and hereditary cancer risk factors, physical examination, and standard biologic tests, an initial workup adapted to sex and age should include low-dose chest computed tomography in heavy smokers, colonoscopy, prostate-specific antigen testing, and mammography. If malignancy is not detected on initial screening, these...
patients should be closely followed because of the long-term risk for cancer occurrence.

Other Carcinoma-Associated Glomerulopathies

In 1984, Mustonen et al. reported that malignancy was not uncommon among older patients with IgA nephropathy. Of 26 patients aged 60 or older, 6 (23%) had cancer compared with none of the 158 patients younger than age 60 (22). Any IgA nephropathy in a patient older than 60 years should prompt a search for a solid tumor, especially in the respiratory tract, the buccal cavity, and the nasopharynx (22). However, this association can be fortuitous or be strengthened by alcoholism, which is a risk factor for both hepatopathy-induced IgA nephropathy and cancers of the upper respiratory tract.

An association between IgA nephropathy and renal cell carcinoma has also been described. IgA nephropathy in a patient older than 60 years should prompt a search for a solid tumor, especially in the respiratory tract, the buccal cavity, and the nasopharynx (22). However, this association can be fortuitous or be strengthened by alcoholism, which is a risk factor for both hepatopathy-induced IgA nephropathy and cancers of the upper respiratory tract.

Paraneoplastic Henoch-Schönlein purpura (HSP) should be suspected when IgA nephropathy is associated with necrotic skin lesions in the absence of cryoglobulin. Compared with age-matched controls, patients with HSP have an increased relative risk (5.25) for malignancy (24). Pertuiset et al. reviewed 19 cases of suspected malignancy-associated HSP; 37% of them had a hematologic malignancy and 63% a solid tumor. In most cases, however, no conclusive evidence showed that HSP was a paraneoplastic syndrome (25). In a retrospective review of 250 patients, Pillebout et al. showed a mortality rate of 26% during a 15-year period of follow-up; cancer was the primary cause, accounting for 27% of deaths, and there was no correlation with immunosuppressive treatment. Cancers preferentially involved the lung (14%) and upper respiratory and digestive tracts (8%) (26).

Several reports suggest an association between rapidly progressive GN and malignancies, with a prevalence of cancer between 7% and 9% (27,28). A variety of tumors have been described (10). Renal cell carcinomas were more common in a retrospective comparison of 477 patients with granulomatosis with polyangiitis and 479 patients with rheumatoid arthritis (odds ratio, 8.73), but the link between renal neoplasia and granulomatosis with polyangiitis remains unclear (29). The increased risk for malignancy has been confirmed in a recent retrospective review of 200 patients with ANCA-associated vasculitis, demonstrating a significantly increased relative risk (6.02) compared with age-matched controls (24). However, tumors occurred up to 512 months after the diagnosis of ANCA-associated vasculitis, and thus the paraneoplastic nature remains uncertain (because cancer could be a side effect of the cytotoxic treatment).

AA-type amyloidosis is found in approximately 3% of renal cell carcinomas (30). Of all carcinomas associated with
amylloidosis, 25%–33% are renal cell carcinomas, although this tumor accounts for only 2%–3% of all carcinomas. The pathophysiology could involve an excessive production of IL-6 by renal tumor cells responsible for chronic inflammation. Remission of the nephrotic syndrome can be achieved by nephrectomy.

Membranoproliferative GN (MPGN) and minimal-change disease also occur in patients with carcinoma, although these lesions are more typical of lymphoproliferative disorders (10,31). The number of observations is too small to allow us to conclude that a causal relationship exists between carcinoma and the renal disease, except for minimal-change disease and thymoma (32). Two thirds of the patients presented with minimal-change disease, sometimes occurring later after curative treatment of thymoma (range, 8–180 months) and remaining steroid sensitive in most cases.

Hematologic Malignancy-Induced Paraneoplastic Glomerulopathies

Hodgkin Disease

The prevalence of glomerulopathy in Hodgkin lymphoma has been studied in two large series comprising 1700 patients, which showed minimal-change disease in 0.4% and AA amyloidosis in 0.1% (33,34). Amyloidosis occurred in late, inflammatory stages of the disease in the absence of an M-component (35). Its markedly reduced incidence is most likely attributable to the rapid remission of the hematologic malignancy induced by modern treatment protocols.

At present, minimal-change disease is the most frequent paraneoplastic manifestation of classic Hodgkin lymphoma. The nephrotic syndrome usually appears early, revealing the lymphoma in about 40% of cases, and displaying a high frequency of steroid resistance (50%) and cyclosporine resistance (36). Effective treatment of classic Hodgkin lymphoma generally induces simultaneous remission of nephrotic syndrome whatever the therapeutic strategy, even without corticosteroids. Nephrotic syndrome usually relapses simultaneously with the hematologic malignancy, remaining highly responsive to specific treatment for the cancer. Minimal-change disease can occur at the time of relapse even if it was initially absent, emphasizing the need to evaluate proteinuria during the follow-up of classic Hodgkin lymphoma. Between-disease interval can be as long as 156 months (36). No particular subgroup of patients with classic Hodgkin lymphoma seems to be at higher risk for minimal-change disease with respect to age, sex, or disease stage (except for systemic symptoms and inflammatory syndrome, which occur more frequently). Minimal-change disease seems to be more frequent in classic Hodgkin lymphoma that exhibits a mixed cellularity and is of the nodular sclerosing subtype (36,37). The pathogenesis of minimal-change disease seems to involve a putative circulating factor secreted by T lymphocytes, leading to cytoskeleton disorganization and heavy proteinuria (38). A new gene named for c-maf–inducing protein (c-mip) has recently been isolated (39). During primary nephrotic syndrome, c-mip increases in the podocytes and turns off podocyte signaling by preventing the interaction of nephrin with the tyrosine kinase Fyn, thereby decreasing nephrin phosphorylation. Moreover, c-mip inhibits interactions between Fyn and neural Wiskott Aldrich syndrome protein and between Neck and nephrin, potentially accounting for cytoskeletal disorganization and the effacement of foot processes (40). Audard et al. demonstrated that c-mip was selectively induced both in podocytes and in Hodgkin and Reed-Sternberg cells in patients with classic Hodgkin lymphoma–associated minimal-change disease but not in patients with isolated classic Hodgkin lymphoma, suggesting its potential involvement in the pathogenesis of this association (Figure 4) (41).

Other glomerulopathies have been associated with classic Hodgkin lymphoma but remain anecdotal (11,42).

Chronic Lymphocytic Leukemia, Related B Cell Lymphomas, and Waldenström Macroglobulinemia

B cell hematologic malignancies can be responsible for the production of small amounts of a monoclonal immunoglobulin whose detection in serum or urine is greatly facilitated by sensitive techniques, such as immunofixation and immunoelectrophoresis. However, these tests fail to detect an M-component in some patients. The newer nephelometric free light chain immunoassay, which can detect free light chains at very low concentrations (43), suggests monoclonality through an increase or decrease in the k-to-l ratio (44) and is useful for monitoring the activity and response to treatment. Another diagnostic approach to monoclonality is the careful analysis of the biopsy specimen with anti–light chain isotype antibodies and anti–γ heavy-chain subclass antibodies. The finding of monotypic deposits should lead investigators to analyze their organization by electron microscopy.

The coexistence of chronic lymphocytic leukemia (CLL) and nephrotic syndrome was first described by Scott in 1957 (45). The prevalence of nephrotic syndrome in patients with CLL is 1%–2% (46). The CLL-associated glomerulopathies generally fulfill the three criteria of a paraneoplastic syndrome. First, they often reveal CLL with a simultaneous diagnosis of both diseases in about 50% of patients. Second, improvement of GN is mainly due to control of hematologic disease, as shown by the first series of 13 cases demonstrating remission of the nephrotic syndrome with chlorambucil alone, a drug ordinarily not effective in idiopathic MPGN and MN (47). Third, the link between CLL and GN is the dysproteinemia produced by the B cell clone, either a cryoglobulin or a noncryoprecipitating M-component, detected in about half of patients. Such a high percentage contrasts with its low incidence in CLL without renal involvement (5%–10%).

The most common lesions are MPGN and MN (11,47). Several mechanisms may be involved (Table 1). First, MPGN can be caused by cryoglobulinemia, predominantly a mixed type II cryoglobulin involving a monoclonal IgM with rheumatoid factor activity and polyclonal IgG (49), although type I cryoglobulin composed of a single monoclonal immunoglobulin can also be implicated.

Second, monotypic immunoglobulin deposits can occur in the absence of cryoglobulinemia and complement activation. Some patients present with features typical of monoclonal immunoglobulin deposition disease (MIDD; see following section on plasma cell dyscrasias) first described by Randall and associates (50), whereas others show an atypical form of MN or MPGN corresponding to an immunotactoid glomerulopathy (Table 1 and Figure 2).
At variance with MIDD, in which the deposits display a nonorganized granular pattern, deposits in immunotactoid glomerulopathy are organized with a microtubular aspect and are restricted to the glomerulus. Similar organized deposits with microtubule formation can be found in leukemic lymphocytes and glomeruli, as demonstrated by Bridoux et al. (51). These authors proposed the term glomerulonephritis with organized microtubular monoclonal immunoglobulin deposition.
Rare patients have a noncryoglobulinemic proliferative GN with nonorganized monoclonal immunoglobulin deposits, a new entity recently described by Nasr et al. with the acronym PGNMID (Table 1) (48,52). At variance with MIDD, in which deposits predominate along tubular basement membranes and cell proliferation is usually mild or absent, PGNMID is a proliferative GN in which deposits are confined to the mesangium and the glomerular basement membrane (Figure 2); hence, the term non–Randall-type proliferative GN is also used for this entity. Although no case of CLL and related B cell lymphoma was reported in the first series (48,52), 9 of 26 patients with noncryoglobulinemic GN and monoclonal immunoglobulin deposits recently reported by Guiard et al. featured an overt hematologic malignancy (53). Among them, one patient had CLL, two had myeloma, and two had non-Hodgkin lymphoma with nonorganized electron-dense deposits fulfilling the definition of PGNMID. Histologic studies showed a striking correspondence between the localization of IgG deposits, defining MPGN or MN histologic patterns, and the subclass of the monoclonal IgG found in the deposits, with a predominance of IgG3 in MPGN and IgG1 in MN. In PGNMID with MPGN pattern, a monoclonal IgM can also be found (54). Among the 28 patients with monoclonal gammopathy and MPGN reported by Sethi et al. (54), 2 patients showed CLL, 1 showed lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (WM), 3 showed low-grade B cell lymphoma, and 6 showed myeloma. The remaining 16 cases featured the characteristics of monoclonal gammopathy of undetermined significance, which, in this context, should instead be called monoclonal gammopathy with related MPGN (54).

In a third group of patients presenting with various glomerular lesions and neither cryoglobulin nor monoclonic glomerular deposits, a clear-cut pathophysiologic link between CLL and the glomerulopathy could not be established (47).

WM-related glomerulonephritides include characteristic intracapillary deposits of IgM (with or without cryoglobulinemia) and AL-amyloidosis (55). Subsequent case reports described immunotactoid glomerulopathy and nonamyloid fibrillary glomerulopathy (56,57), cryoglobulinemia-related GN (58), crescentic GN (59,60), light-chain deposition disease (LCDD) (61), and MPGN without cryoglobulinemia (62). The incidence of renal involvement of malignant IgM-secreting proliferation has decreased, mostly because of improved treatment of WM, the major cause of those nephropathies. Audard et al. (62), who recently revisited the disease spectrum, showed that GN with intracapillary thrombi of IgM, originally described by Morel-Maroger et al. as Waldenström macroglobulinemic glomerulonephritis (59), was not specific for WM and suggested that the term intracapillary monoclonal deposits disease may be more appropriate in this context.

### Plasma Cell Dyscrasias

Since the first description of immunoglobulin amyloidosis by Glenner et al. in 1971 (63), the spectrum of glomerular diseases occurring in patients with plasma cell dyscrasias has expanded dramatically. On the basis of the distribution of the deposits, these diseases can be classified into two categories by electron microscopy (Table 2).

The most frequent glomerulopathy in plasma cell dyscrasias is AL-amyloidosis, found in about 5%–11% of patients with myeloma at autopsy, whereas the prevalence of LCDD is 3%–5% (64,65). MIDD differs from amyloidosis in that the granular deposits lack affinity for Congo red and do not have a fibrillar organization (66).

Myeloma is found in approximately 50% of patients with LCDD or light- and heavy-chain deposition disease and in approximately 25% of those with heavy-chain deposition disease (HCDD). In some patients who presented with “common” myeloma and normal-sized monoclonal immunoglobulin without kidney involvement, LCDD occurred when the disease relapsed after chemotherapy, together with immunoglobulin structural abnormalities (67). Because melfalan may induce immunoglobulin 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 WM, CLL, and nodal marginal-zone lymphoma (68). Like AL-amyloidosis, MIDD can also occur in the absence of a detectable malignant process, even after prolonged follow-up (>10 years), illustrating that “paraneoplastic-like glomerulopathies” can occur with benign proliferation. A monoclonal bone marrow plasma cell population then is easily detectable by immunofluorescence examination.

The pathogenesis of MIDD involves the kidney deposition of monoclonal immunoglobulin subunits; however, in contrast to amyloidosis, deposition induces a dramatic accumulation of extracellular matrix that is responsible for glomerular and tubular basement membrane thickening.

<table>
<thead>
<tr>
<th>Table 2. Pathologic classification of diseases with tissue deposition or precipitation of monoclonal immunoglobulin-related material</th>
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<tbody>
<tr>
<td><strong>Organized</strong></td>
</tr>
<tr>
<td>Crystals</td>
</tr>
<tr>
<td>Myeloma cast nephropathy</td>
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<tr>
<td>Fanconi syndrome</td>
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<tr>
<td>Other (extrarenal)</td>
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nodular glomerulosclerosis, and interstitial fibrosis. Unusual properties of light chains are involved in LCDD and amyloidosis (Table 3) (66). In LCDD and AL-amyloidosis, light chains are supposed to bind to an as-yet unidentified common caveolae-associated receptor and to induce divergent phenotypic transformation of mesangial cells in relation to distinct cellular trafficking of LCDD and AL-amyloid light chains, as shown in Figure 5 (69,70). In

Table 3. Light-chain peculiarities associated with amyloidosis and light-chain deposition disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>AL-Amyloidosis</th>
<th>Light-Chain Deposition Disease</th>
</tr>
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<tbody>
<tr>
<td>Predominant isotype</td>
<td>λ</td>
<td>κ</td>
</tr>
<tr>
<td>Variability subgroup</td>
<td>$V_{\text{A}}$I$^a$</td>
<td>$V_{\text{A}}$IV$^a$</td>
</tr>
<tr>
<td>Size abnormalities</td>
<td>Fragments in urine</td>
<td>Short or large light chains</td>
</tr>
<tr>
<td>Amino acid residues exposed to solvent</td>
<td>Acidic</td>
<td>(glycosylation)$^b$</td>
</tr>
<tr>
<td>Interaction with</td>
<td>Extracellular matrix components$^c$</td>
<td>Hydrophobic</td>
</tr>
</tbody>
</table>

From reference 11, with permission.

$^a$All $V_{\text{A}}$I light chains are amyloidogenic. Not all $V_{\text{A}}$IV light chains induce light-chain deposition disease.

$^b$Glycosylation correlates with the lack of circulating and urinary light chains by sensitive detection techniques, as observed in about 20% of patients with light-chain deposition disease.

$^c$Reactivity with extracellular matrix components may be explained by high dimerization constant and antibody-like behavior of the V-domain.

Figure 5. Interactions between mesangial cells and glomerulopathic light chains and mesangial matrix alterations. Light chain deposition disease–light chains (LCDD-LCs) interact with surface receptors on cells and are metabolized in the early endosomes. AL-amyloidosis–light chains (AL-Am-LCs) are endocytosed avidly and processed in the mature lysosomes, resulting in opposing TGFβ, extracellular matrix (ECM), and matrix metalloproteinase (MMP) alterations. MMP secretion and expression are increased by human mesangial cells (HMCs) in AL-amyloidosis and are decreased in LCDD HMCs. HMCs incubated with LCDD–light chains acquire a well developed rough endoplasmic reticular system and transform into myofibroblasts, whereas HMCs incubated with amyloidogenic light chains transform into a macrophage phenotype, acquiring numerous lysosomes and losing their normal smooth muscle features. From reference 70, with permission.
HCDD, deletion of the first constant domain C1 of k light-chain deposition disease (LCDD) is required for secretion of free heavy chains, which are rapidly cleared from the circulation by organ deposition (71).

Clinical manifestations of MIDD are summarized in Table 4. In HCDD, the higher prevalence of hypertension, nephrotic syndrome, and hematuria might be explained by the greater severity of renal lesions. Liver and cardiac involvement occur in approximately 25% of patients with LCDD and LHCD, thereby increasing the risk for death (72). Extrarenal deposits are less common in patients with HCDD (66).

Treatment is aimed at reducing immunoglobulin production (93). The outcome of patients with MIDD has improved, as recently reported by Nasr et al. (78). This improvement results from earlier diagnosis and more potent chemotherapeutic regimens, including stem cell transplantation; stem cell transplants are now challenged by new drugs, such as bortezomib (93). Survival from onset of symptoms varies from 1 month to 10 years. As in other paraneoplastic syndromes, glomerular lesions can regress in patients who undergo complete remission of their hematologic malignancy (93,94).

AL-amyloidosis has been extensively reviewed in recent publications (94,95).

Myeloproliferative Neoplasms
Glomerulopathies have occasionally been reported in patients with myeloproliferative neoplasm (MPN). A first small series in 1999 showed FSGS and mesangial sclerosis (96). Said et al. recently reported on a series of 11 patients with MPN who developed proteinuria and renal insufficiency (97). Kidney biopsy revealed a peculiar form of glomerulopathy called MPN-related glomerulopathy, characterized by a combination of mesangial sclerosis and hypercellularity, segmental sclerosis, features of chronic thrombotic microangiopathy, and intracapillary hematopoietic cell infiltration. Most patients (73%) had primary myelofibrosis, a disease that is less common than polycythemia vera, essential thrombocythemia, and chronic myelogenous leukemia, suggesting that patients with primary myelofibrosis are more at risk of developing MPN-related glomerulopathy. This entity is, however, not considered a pure paraneoplastic disease because of the presence of hematopoietic cell infiltration.

Table 4. Comparison of clinical manifestations, renal lesions, and hematologic features in patients with monoclonal immunoglobulin deposition disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCDD/LHCD(^a)</th>
<th>HCDD(^b)</th>
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<tr>
<td>Male-to-female ratio</td>
<td>1.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Age (range) (yr)</td>
<td>57 (22–94)</td>
<td>55 (26–79)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>66</td>
<td>91</td>
</tr>
<tr>
<td>Renal failure (serum creatinine ≥ 130 μmol/L) (%)</td>
<td>98</td>
<td>88</td>
</tr>
<tr>
<td>Nephrotic syndrome(^c) (%)</td>
<td>32</td>
<td>51</td>
</tr>
<tr>
<td>Hematuria (%)</td>
<td>53</td>
<td>85</td>
</tr>
<tr>
<td>Nodular glomerulosclerosis (%)</td>
<td>31–100</td>
<td>94</td>
</tr>
<tr>
<td>Multiple myeloma (%)</td>
<td>55</td>
<td>24</td>
</tr>
<tr>
<td>M-component (blood or urine) (%)</td>
<td>85</td>
<td>69(^d)</td>
</tr>
</tbody>
</table>

LCDD, light-chain deposition disease; LHCD, light- and heavy-chain deposition disease; HCDD, heavy-chain deposition disease.

\(^a\)Patients are from the series described in references 72–78.

\(^b\)Cases are from references 66,76,78–92.

\(^c\)Proteinuria ≥3 g/d.

\(^d\)Including two cases with only free k chain.

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