A Case of Atypical Light Chain Deposition Disease—Diagnosis and Treatment

David J. Salant,* Vaishali Sanchorawala,† and Vivette D’Agati‡
*Renal Section, Department of Medicine and †Stem Cell Transplantation Program, Section of Hematology/Oncology, Boston University Medical Center, Boston, Massachusetts; and ‡Department of Pathology, Columbia University College of Physicians and Surgeons, New York, New York

Clinical Conference

A New Feature of CJASN for Clinicians

Joining the outstanding original research and invited materials already appearing in the Clinical Journal of the American Society of Nephrology (CJASN), a new feature, Clinical Conferences, appears for the first time in this issue. This feature is designed to expand our emphasis on practical information for clinicians and is organized and edited by Ajay Singh of Brigham and Women’s Hospital and by Charles Alpers of the University of Washington. We will periodically publish Clinical Conferences from academic health centers where expert clinicians discuss a particularly challenging case. This issue’s inaugural Conference on light chain deposition disease is discussed by David Salant, Vaishali Sanchorawala, and Vivette D’Agati. This new Clinical Conference feature will supplement CJASN’s published versions of the ClinicoPathologic Conference (CPC) and Nephrology Quiz that are presented each year at the annual meeting of the American Society of Nephrology. You will see these articles in subsequent issues. By providing these features, CJASN hopes to make analyses as well as diagnostic and therapeutic approaches by acknowledged experts accessible to clinicians. We sincerely hope that our readers enjoy this new feature as well as the annual CPC and Nephrology Quiz. CJASN’s entire editorial team would also like to thank the readership for their support of the journal. We look forward to receiving feedback on the CJASN Clinical Conference.

William M. Bennett, MD
Harold I. Feldman, MD
Mohamed H. Sayegh, MD

Case Presentation

The patient is a 70-yr-old retired schoolteacher who had been in good health until he was found to have asymptomatic proteinuria (approximately 1 g/24 h) on routine physical examination. He was mildly hypertensive, and serum creatinine was 1.2 mg/dl. There was no monoclonal paraprotein (gammopathy) detected on serum protein electrophoresis, and cryocrit was 33.4 mg/dl). There was no cellular casts. Urine protein electrophoresis was not performed.

The patient’s past medical history was significant for mild hypertension, hyperlipidemia, diet-controlled glucose intolerance (HbA1c 5.2), an intentional weight loss of 15 lb over 12 mo, resolved Bell’s palsy, resolved hypothyroidism, skin cancer resection, a previous diskectomy, and bilateral total knee replacements within 6 mo of this presentation with excellent results. His medications included atorvastatin, metoprolol XL, tamsulosin, and aspirin. He had not taken any nonsteroidal anti-inflammatory drugs for over 6 mo. Irbesartan was added because of the proteinuria.

Four weeks later, the patient presented with a 20-lb weight gain and generalized swelling. He had no new symptoms other than discomfort from fluid retention. The review of systems at the time was entirely negative. On examination, he appeared healthy, but his BP was 212/90 with a pulse rate of 60/min. He had generalized anasarca. His physical examination was otherwise completely normal. In particular, he had no rash, lymphadenopathy, organomegaly, macroGLOSSIA, or telangiectasias, and his joints appeared normal.

Urinalysis showed lipiduria, occasional red blood cells, and no cellular casts. Urine protein excretion was 7 g/24 h, and serum albumin was 3.1 g/dl. Serum creatinine was 1.4 mg/dl, hemoglobin was 11.6 g/dl, white blood cell count was 5600, and platelets were 242,000. Serum complement C3 was reduced to 74 mg/dl (normal 80 to 170), and C4 was normal at 25 mg/dl and his joints appeared normal.

Renal ultrasound showed normal-sized kidneys without evidence of hydronephrosis. Subsequent laboratory studies showed negative anti-nuclear antibody and anti dsDNA, negative serology for hepatitis B and C, and normal quantitative Ig levels (IgG 700 mg/dl, IgA 165 mg/dl, and IgM 33.4 mg/dl). There was no monoclonal paraprotein (gammopathy) detected on serum protein electrophoresis, and cryocrit was <1%. Urine protein electrophoresis was not performed. Diuretics and antihypertensives were added to the patient’s treatment regimen.

Differential Diagnosis

The differential diagnosis in a case such as this presenting with recent onset of severe nephrotic syndrome, hypertension, and renal insufficiency is broad and includes the conditions shown in Table 1. Hypocomplementemia is typically seen in immune complex diseases such as postinfectious glomerulonephritis, lupus nephritis, membranoproliferative glomerulonephritis (MPGN) type 1 with or without mixed cryoglobulinemia, and...
sometimes immunotactoid glomerulonephritis. The normal C4 suggests that there may be activation of the alternate pathway of complement as is seen in dense deposit disease (MPGN type 2); however, this would be distinctly unusual in a 70-yr-old man. A renal biopsy was performed.

Renal Biopsy Findings
Among the 19 glomeruli sampled for light microscopy, three were globally sclerotic. Glomeruli appeared enlarged with mild segmental increase in mesangial matrix and marked diffuse thickening of glomerular basement membranes (GBM). The glomerular capillary walls were thickened by large subendothelial deposits that stained brightly eosinophilic material associated with segmental mesangial interposition. There is mild mesangial expansion, without mesangial hypercellularity or nodularity. Magnification, ×400 (hematoxylin and eosin).

Table 1. Clinical differential diagnosis of nephrotic syndrome, hypertension, and renal insufficiencya

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<thead>
<tr>
<th>Diagnosis</th>
<th>Antigens</th>
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<tr>
<td>FSGS</td>
<td>Collapsing glomerulopathy</td>
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<tr>
<td>Membranous nephropathy</td>
<td>MPGN type 1, primary or secondary</td>
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<tr>
<td>Mixed cryoglobulinemia</td>
<td>Dense deposit disease (MPGN type 2)</td>
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<td>Lupus nephritis</td>
<td>IgA nephropathy</td>
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<td>Amyloidosis</td>
<td>Fibrillar glomerulonephritis</td>
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<tr>
<td>Immunotactoid glomerulonephritis</td>
<td>Light or heavy chain deposition disease</td>
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Figure 1. A representative glomerulus shows global thickening of the glomerular basement membranes (GBM) by glassy eosinophilic material associated with segmental mesangial interposition. There is mild mesangial expansion, without mesangial hypercellularity or nodularity. Magnification, ×400 (hematoxylin and eosin).

Figure 2. The GBM are thickened by ribbon-like deposits of highly periodic acid Schiff (PAS)-positive material producing an irregular inner subendothelial aspect. Magnification, ×600.

Material staining, suggesting deposits. There was mild to moderate arteriosclerosis. No vascular immune deposits were identified with the special stains. Congo red stain for amyloid was negative.

Direct immunofluorescence performed on cryostat sections revealed 3+ diffuse linear staining for κ light chain involving glomerular and tubular basement membranes, with negative λ light chain (Figure 4). Trace to 1+ linear staining for IgG and 1+ linear albumin were seen in the same distribution. Glomeruli also showed 2+ granular to semilinear global glomerular capillary wall staining for C3 (Figure 5), with trace C1q. Casts stained equally (1+) for κ and λ light chains. Immunohistochemical stains for κ and λ performed on paraffin tissue showed strong positivity for κ light chain, with negative staining for λ, in the distribution of GBM, mesangium, and tubular basement membranes (Figure 6).

Electron microscopic evaluation showed massive thickening of glomerular capillary walls by large subendothelial electrondense deposits (Figure 7). These deposits exhibited a punctate granular (nonfibrillar) texture and appeared to be deposited on a background of extracellular matrix material with scalloped, wavy contours (Figure 8). In some glomerular capillaries, the subendothelial deposits had a slightly lamellated appearance, suggesting successive layers of deposition (Figure 8). Partial
mesangial interposition was seen in some of these areas. Similar punctate electron-dense deposits were present in the mildly expanded mesangial matrix but without nodule formation. Foot process effacement involved approximately 75% of the glomerular capillary surface area. The tubular basement membranes appeared thickened and lamellated, containing ill-defined granular electron-dense deposits, most prominently at the outer interstitial interface. Proximal tubular cells contained intracytoplasmic protein resorption droplets. The diagnosis from renal biopsy was atypical light chain deposition disease (LCDD) with massive glomerular subendothelial deposits and mild membranoproliferative features.

Subsequent Course and Laboratory Findings
In follow-up to the renal biopsy findings, a bone marrow biopsy was performed that showed a normocellular marrow with no evidence of myeloma. Flow cytometry of the bone marrow aspirate showed 4% monoclonal plasma cells. Urine immunofixation electrophoresis showed bands of restricted mobility in the IgG and k region. These findings were considered to be consistent with a monoclonal gammopathy of uncertain significance.

Two months later, the patient was referred to Boston University Medical Center, at which time he was complaining of fatigue, anorexia, weakness, and concern about declining renal function. He had lost 30 lb with diuresis and aged markedly since the onset of his illness. He had no bone pain or bleeding. His BP was 190/85 on four antihypertensive medications and two diuretics. He had persistent anasarca but no other relevant physical abnormalities. Serum creatinine was 2.7 mg/dl, blood urea nitrogen was 93 mg/dl, and albumin was 2.7 g/dl. Immunofixation electrophoresis of serum and urine revealed the presence of a monoclonal IgG k gammopathy (Figure 9). Repeat bone marrow biopsy with immunohistochemistry showed 10% k clonal plasma cells with normal hematopoietic elements and no evidence of multiple myeloma (Figure 10). Serum free light chain assay (Freelite; the Binding Site, San Diego, CA) showed markedly elevated free k of 1232 mg/L (normal 3.3 to 19.4) and a free k:λ ratio 23.56 (normal 0.26 to 1.65). The constellation of these findings was diagnostic of a k clonal plasma cell dyscrasia.

Treatment
The patient was offered treatment with high-dose intravenous melphalan and autologous stem cell transplantation (1). Hematopoietic stem cells were mobilized with granulocyte colony-stimulating factor as described previously (2). A total of 3.8 × 10⁶ CD34⁺ cells/kg were collected. Stem cell mobilization and collection were complicated by refractory anasarca, decline in functional status, rapid atrial fibrillation, and deterioration of renal function with serum creatinine rising to 4.7 mg/dl. Because of the impaired renal function, he received a modified high-dose melphalan regimen at 100 mg/m² (rather than the standard dose of 200 mg/m²), followed by autologous stem cell transplantation. In addition to the expected myeloablation, worsening renal function, anasarca, and emesis complicated the posttransplantation period. He had prompt engraftment of neutrophils and platelets 11 and 13 d after stem cell transplantation, respectively, followed by gradual improvement in his

Figure 4. Immunofluorescence reveals strong global linear staining of glomerular capillary walls (with frequent double contours) and diffuse linear staining of tubular basement membranes in a regular distribution for k light chain (left), with negativity for λ (right). Magnification, ×100.
When seen at his 5-mo follow-up visit, he had achieved a complete hematologic response with normalization of serum free light chain (κ:λ ratio 1.5; Figure 11) and improvement of his exercise tolerance and renal function with serum creatinine of 3.1 mg/dl. Although he was still proteinuric, he had lost 30 lb of fluid weight, pleural effusions present at the time of discharge had resolved, and serum albumin had improved to 3.5 g/dl (Figure 11). BP was 115/60 without postural change on labetalol and bumetanide.

**Clinical Discussion (Dr. David Salant)**

In summary, here we describe the case of a patient who presented with nephrotic syndrome, severe hypertension, and progressive renal failure and whose glomeruli showed a membranoproliferative pattern on renal biopsy with extensive subendothelial deposits. Immunofluorescence microscopy revealed isolated κ light chains, thus establishing the diagnosis of LCDD. This was confirmed by an elevated ratio of κ/λ free light chains in the serum and urine and a predominance of κ light chain–positive plasma cells on bone marrow biopsy.

Monoclonal Ig deposition diseases (MIDD) most often occur in the sixth and seventh decades of life, but patients in the 20s and 90s have been reported (3–5). Both genders and all races may be affected. The kidneys are almost universally affected in LCDD (3–5). Severe albuminuria is the rule. Nephrotic syndrome is present in approximately 30% of cases, and microscopic hematuria is common. Hypertension occurs frequently and may be severe, as in this case. Renal failure develops in most cases over the course of weeks to years. In addition, acute renal failure may occur from tubulointerstitial deposits and inflammation (6). In addition to the glomerular deposition of light chains, LCDD may be associated with myeloma cast nephropathy, which may also contribute to the development of acute renal failure (4). Greater than 60% of cases progress inexorably to end-stage renal failure, regardless of whether they are treated with conventional chemotherapy (3). Historically, 5-yr patient survival is <50% and is influenced adversely by associated multiple myeloma (present in 40 to 60% of cases) and extrarenal LCDD (4,5,7).

**Extrarenal Manifestations of LCDD**

Organs affected by extrarenal LCDD are shown in Table 2. Of these, the liver is quite commonly affected and may present with cholestatic jaundice, portal hypertension, and occasionally hepatic failure (8–11). Cardiac manifestations include restrictive cardiomyopathy and myocardial infarction from light chain deposits in the coronary vasculature (4,12,13). Other manifestations include cerebral infarction and hemorrhage, peripheral neuropathy, and mononeuritis multiplex. Adrenal insufficiency has also been reported.

**Recurrence after Renal Transplantation**

Without effective treatment, LCDD recurs almost universally after renal transplantation, and recurrence may occur within weeks to years after transplantation. This is highlighted by the Mayo Clinic experience (14). Of seven patients with LCDD who received kidney transplants, one died 3 mo after transplantation and the disease recurred in five of the remaining six patients within 2 to 45 mo. Four of these patients subsequently died, and one was on dialysis at the time of the report. Only one patient remained recurrence-free after 13 yr, and the authors concluded that “kidney transplantation should not be an option for LCDD patients unless measures have been taken to reduce light chain production” (14).
The two Ig light chain isotypes (\(\text{LHCDD}\)). By contrast, staining for a single class of heavy chain restriction defines light and heavy chain deposition disease (HCDD). In our case, the staining for monoclonal light chain (7,15). Three subgroups have been described. Linear staining for monoclonal light chain (\(k\) or \(\lambda\)) defines LCDD. Staining for a single class of Ig heavy chain (\(\gamma\), \(\alpha\), or \(\mu\)) with light chain restriction defines light and heavy chain deposition disease (LHCD). By contrast, staining for a single class of heavy chain (\(\gamma\), \(\alpha\), or \(\mu\)) with no corresponding light chain occurs in heavy chain deposition disease (HCDD). In our case, the staining for \(k\) light chain, without staining for Ig heavy chain or \(\lambda\) light chain, was consistent with the most common variety, \(k\) LCDD.

The vast majority of cases of LCDD (approximately 80%) are of \(\kappa\) isotype (5). For example, in the Columbia experience, among 23 cases of pure MIDD (without overlap with myeloma cast nephropathy), 12 were LCDD (11 \(k\), one \(\lambda\)), five were LHCD (three IgG\(\kappa\) and two IgG\(\lambda\)), and six were HCDD (five \(\gamma\), one \(\alpha\)) (7). By immunofluorescence, among the 23 cases of MIDD, 100% had diffuse tubular basement membrane staining, 87% had GBM staining, and 83% had mesangial staining. Thus linear diffuse staining of tubular basement membranes appears to be the most consistent immunofluorescence finding. However, at the ultrastructural level, 100% of cases exhibited GBM deposits, with 96% mesangial deposits and 96% tubular basement membrane deposits. These differences probably reflect in part the variations in sampling by and sensitivity of these techniques. By electron microscopy, the deposits typically have a delicate punctate granular (nonfibrillar) highly electron-dense appearance that appears to pepper the renal basement membranes. By light microscopy, most cases exhibit nodular glomerulosclerosis, sometimes associated with mild membranoproliferative features, without significant GBM thickening. Thickening of tubular basement membranes and vascular basement membranes can be observed by light microscopy as strongly PAS-positive ribbons of deposition along tubular basement membrane deposits and surrounding medial myocytes. This constellation of immunofluorescence, ultrastructural, and histologic abnormalities defines MIDD and must be differentiated from the isolated linear staining of renal basement membranes for monoclonal light chain that is occasionally observed in renal biopsies from patients with M spike who lack evidence of structural or functional renal disease.

The case reported here was atypical in that the glomerular deposition did not produce a nodular mesangial sclerosing pattern but caused massive thickening of the glomerular capillary walls, associated with a membranoproliferative pattern. Differential diagnosis of the membranoproliferative pattern in dysproteinemia-related renal disease is listed in Table 3. Among the entities listed in Table 3, the only one that gives
linear immunofluorescence staining of tubular basement membranes for the pathogenic light chain, without associated heavy chain, is LCDD. Cryoglobulinemic glomerulonephritis and Waldenstrom’s macroglobulinemic glomerulonephritis usually exhibit intracapillary deposits (forming protein thrombi) with prominent glomerular infiltration by monocytes/macrophages (16). Immunotactoid glomerulonephritis classically has a heavy and light chain component and exhibits an organized microtubular substructure by electron microscopy (17). The newly described entity of proliferative glomerulonephritis with monoclonal IgG deposits mimics ordinary immune complex–mediated glomerulonephritis (typically membranoproliferative with or without a membranous component) and displays granular electron-dense deposits in subendothelial as well as possible subepithelial and mesangial locations (18). The deposits stain for γ heavy chain and a single light chain component and exhibits an organized microtubular substructure by electron microscopy (17). The newly described entity of proliferative glomerulonephritis with monoclonal IgG deposits mimics ordinary immune complex–mediated glomerulonephritis (typically membranoproliferative with or without a membranous component) and displays granular electron-dense deposits in subendothelial as well as possible subepithelial and mesangial locations (18). The deposits stain for γ heavy chain and a single light chain component and exhibit Gκ (IgG1–IgG4) restriction (18).

Another atypical feature of this case of LCDD was the staining for complement components C3 (2+) and C1 (trace), with reduction in serum C3. Complement deposition in glomerular and tubular basement membranes leading to reduced serum complement levels is not uncommon in HCDD and may also be observed in LHCDD owing to complement activation on the γ constant heavy (CH)2 domain (7,19,20). However, no such γ heavy chain component could be demonstrated in our case by immunofluorescence. The staining for IgG was only trace to 1+ and similar in intensity to that of albumin, suggesting background staining. Thus, the mechanism of local and systemic complement activation is unexplained in this case, although the possibility of a truncated γ heavy chain component with unique structural alterations not recognized by commercial antisera to IgG cannot be excluded. Alternatively, uncontrolled Ig-independent activation of the alternative pathway as occurs in dense deposit disease (MPGN type 2) could explain the low serum level of C3 and normal C4 and glomerular deposits of C3 in the absence of γ heavy chain. Possible mechanisms of such activation, such as the presence of C3 nephritic factor or reduced complement regulatory activity (21), were not investigated in our patient.

Pathophysiology of LCDD

Ig diversity depends in part on rearrangement of several gene segments during B cell differentiation. The B cell chooses from among a repertoire of six possible VH subgroups, four Vk subgroups, and six Va subgroups. In hematologic malignancies, such as myeloma or B cell lymphoma, monoclonal Ig, and/or a monoclonal free light chain and/or a monoclonal free (usually truncated) heavy chain may be produced in excess. In the case of LCDD, it is a monoclonal light chain that deposits in tissues and causes pathology in the kidney and other target organs. The pathophysiology of LCDD is closely linked to the unique amino acid sequence of the pathogenic light chain.

Several investigators have characterized the structural and biochemical properties of the light chains produced in patients with LCDD at the cDNA and protein levels (1,22–26). They have found a particularly high representation of the VkIV and VkI variability subgroups. This finding stands in sharp contrast to AL amyloidosis, which is mostly of the VκVI subgroup. Interestingly, the VκIV variability subgroup is a rare subgroup that contains a longer CDR1 loop containing more hydrophobic residues (5). The pathogenic light chains sequenced to date typically exhibit a high rate of unique amino acid substitutions in both the complementarity determining region (CDR) and framework region (FR) that could arise by somatic antibody selection and affinity maturation. Many of these mutations cause increased hydrophobicity by the presentation of nonpolar moieties on the surface of the light chain molecule that is exposed to solvent. Such substitutions would be

Figure 9. Immunofixation electrophoresis of serum and urine revealed a restricted IgG κ band (arrows). MW, bands represent albumin, α-, β-, and γ-globulin from the top down; G, IgG; A, IgA; M, IgM.

Figure 10. Bone marrow biopsy immunohistochemistry with anti-κ (left) and anti-λ (right) light chain antibodies revealed a predominant κ population of plasma cells.
predicted to promote reduced protein solubility, alterations in protein folding, and increased propensity for tissue aggregation (22,24–26). Cogne et al. (22) showed that one particular pathogenic light chain from a patient with LCDD contained a normal constant region and differed from the V\textsubscript{\textalpha} germline gene by nine point mutations, including amino acid substitutions that resulted in potential N-glycosylation sites, which could favor tissue precipitation. In addition to effects on hydrophobicity and glycosylation sites, some of these mutations increase the isoelectric point (pI) of the light chain, potentially promoting charge interactions between the cationic light chain and anionic glycosaminoglycans in basement membranes (26). Once deposited in the glomerulus, the light chains promote mesangial cell transformation to a more myofibroblastic phenotype important in the development of glomerulosclerosis. Mesangial cells exposed \textit{in vitro} to pathogenic light chains of LCDD acquire myofibroblastic markers such as smooth muscle actin and muscle specific actin and exhibit increased synthesis of TGF-\beta and extracellular matrix proteins such as laminin, collagen IV, fibronectin, and tenascin (27,28).

Discussion of Treatment Options (Dr. Vaishali Sanchorawala)

There have been few guidelines for the treatment of MIDD in general and LCDD in particular. In part this was because conventional chemotherapy with oral melphalan and prednisone, as used in multiple myeloma, was found to have little lasting benefit (3). In addition, in the absence of associated multiple myeloma, MIDD were considered a form of monoclonal gammopathy of uncertain significance that did not warrant aggressive chemotherapy, as in the case presented here. However, there has developed an increased awareness of the need for effective therapy, even in the absence of multiple myeloma, because of the dire consequences of renal and other end-organ damage and the high recurrence rate after transplantation. Recently, the use of myeloablative doses of melphalan combined with autologous stem cell transplantation (HDM/SCT), as has been used to treat multiple myeloma (29,30) and systemic AL amyloidosis (2), has been described for patients with both heavy and light chain deposition diseases (1,31,32). These retrospective series demonstrate feasibility and safety of HDM/SCT.

In the largest published series, 11 patients with MIDD were treated with HDM/SCT, 10 of whom had underlying multiple myeloma (31). Hematologic remission was achieved in 55% with a clinical response in 36% of patients. Median follow-up was 51 mo, during which one patient died.

We previously reported our experience with HDM/SCT for the treatment of LCDD in five patients (1). To date, nine patients have been treated for nonamyloid LCDD at Boston University Medical Center. Eligibility criteria for this aggressive treatment with HDM/SCT included a tissue diagnosis with characteristic findings of LCDD; evidence of a clonal plasma cell dyscrasia; age >18 yr; and minimum measures of performance status (Southwest Oncology group 0 to 3), pulmonary function, and cardiac function as described previously (1,2). Patients who required dialysis for LCDD-associated renal failure were not excluded when other eligibility criteria were met. Peripheral blood stem cells were collected following granulocyte colony-stimulating factor mobilization; a minimum yield of $2.5 \times 10^6$ CD34$^+$ cells/kg was required to proceed to HDM. Patients received 100 to 200 mg/m$^2$ intravenous melphalan over 2 d. Patients were followed for hematologic and clinical responses at 3 mo, 6 mo, and annually thereafter. All but one of the patients with LCDD were male, with a median age of 46 yr (range 34 to 70). Seven of these nine patients had a $\kappa$ clonal plasma cell dyscrasia, and all had biopsy-proven renal involvement as well as either proteinuria or elevated serum creatinine concentration. One of these patients (LCDD-$\kappa$) also had cardiac

Table 2. Extrarenal manifestations of LCDD$^a$

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<th>Manifestation</th>
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<tr>
<td>Cardiac (21%)</td>
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<tr>
<td>restrictive cardiomyopathy</td>
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<tr>
<td>myocardial infarction, coronary LCDD</td>
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<tr>
<td>Liver (19%)</td>
</tr>
<tr>
<td>cholestatic jaundice</td>
</tr>
<tr>
<td>hepatic failure</td>
</tr>
<tr>
<td>Cerebral infarction and hemorrhage</td>
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<tr>
<td>Peripheral neuropathy and mononeuritis multiplex</td>
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<td>Adrenal insufficiency</td>
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$^a$Percentages from Pozzi and Locatelli (9). LCDD, light chain deposition disease.

Table 3. Differential diagnosis of MPGN Pattern in dysproteinemia-related renal diseases$^a$

<table>
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<th>Category</th>
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<tbody>
<tr>
<td>MIDD (LCDD, LHCDD, HCDD)</td>
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<tr>
<td>Cryoglobulinemic glomerulonephritis (types 1 or 2)</td>
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<tr>
<td>Waldenstrom’s macroglobulinemic glomerulonephritis</td>
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<tr>
<td>Immunotactoid glomerulonephritis</td>
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<td>Proliferative glomerulonephritis with monoclonal IgG deposits</td>
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$^a$HCDD, heavy chain deposition disease; LHCDD, light and heavy chain deposition disease; MIDD, monoclonal Ig deposition diseases.
involvement evident on endomyocardial biopsy. Two patients had previously received kidney transplants followed by recurrence of LCDD in the transplanted kidney 4 and 7 yr later. Median creatinine clearance before treatment among the non-dialysis-dependent patients was 31 ml/min (range 21 to 149 ml/min). One patient was on hemodialysis. Four patients had received previous chemotherapy with oral regimens. None of the patients had multiple myeloma. The median follow-up of treated patients has been 17 mo (range 4 to 41 mo). Median survival cannot be calculated, because all patients are alive and well. A complete hematologic response, defined as absence of monoclonal gammapathy in serum and urine by immunofixation electrophoresis, bone marrow biopsy showing <5% clonal plasma cells, and normalization of serum free light chain ratio, was achieved in seven (88%) of the eight patients studied. The patient who was dialysis dependent at the time of treatment has had a durable complete hematologic response over 41 mo of follow-up and has undergone kidney transplantation. The median percentage reduction in proteinuria after treatment was 75.3% (range 38.7 to 89.3%) in all patients in whom urine was available for analysis. Some patients also experienced a decline in serum creatinine. Reversal of dialysis-dependent renal failure has also been reported in a patient with LCDD treated with HDM/SCT (32). This is unlike HDM/SCT treatment for primary amyloidosis, in which patients who achieve hematologic remission have a decline in proteinuria but usually do not have improvement in renal function (33).

Thus, HDM/SCT is tolerable and effective in the treatment of LCDD. This form of treatment induces hematologic remissions in a substantial proportion of patients with LCDD and is effective in inducing clinical responses.

Conclusion (Dr. Salant)
In summary, monoclonal Ig deposition should be considered in any adult patient, regardless of age, presenting with otherwise unexplained proteinuria. Immunofluorescence microscopy with specific stains for κ and λ light chains is key to the diagnosis. Although nodular glomerulosclerosis with mesangial expansion is typically observed on light microscopy, atypical patterns may be seen, including diffuse proliferative and membranoproliferative forms of glomerulonephritis. Many cases do not have bone marrow biopsy findings of a malignant plasma cell dyscrasia. Measurement of free κ and λ light chains in the serum and urine is a sensitive way to establish the diagnosis of LCDD and follow the response to therapy; however, in the presence of severe renal dysfunction, the ratio is more useful than the absolute serum levels because renal clearance of the light chains is impaired. Almost all patients progress inexorably to end-stage kidney failure, and recurrence of LCDD is almost universal after renal transplantation. Patient survival is adversely affected by the presence of extrarenal LCDD, especially when the heart is affected. Myeloablative high-dose chemotherapy and autologous stem cell transplantation induce hematologic remission in a high proportion of patients who are eligible for such treatment, and early results from a limited number of patients suggests that the deterioration of renal function may be arrested and possibly reversed. Kidney transplantation should not be undertaken unless a hematologic remission has been induced.

Question and Answer
Dr. Theodore I. Steinman (Professor of Medicine, Harvard Medical School, Renal Division, Beth Israel Deaconess Medical Center, Boston, MA): In my experience, LCDD with a nephrotic syndrome presentation usually occurs in the setting of impaired kidney function. This patient had only a mild increase in serum creatinine. What is your experience with near-normal kidney function with this LCDD scenario?
Dr. Salant: I agree that most patients with LCDD and nephrotic syndrome have or rapidly develop renal dysfunction; however, the literature indicates that patients may present with proteinuria in the absence of overt renal dysfunction (34), and we have seen the diagnosis of LCDD made on renal biopsy in patients presenting with asymptomatic proteinuria. I think it depends on how early one gets to see the patient.

Dr. Jochen Reiser (Assistant Professor of Medicine, Harvard Medical School, Renal Unit, Massachusetts General Hospital, Boston, MA): Have animal models confirmed the importance of the biochemical and/or structural composition of the light chain in determining deposition?
Dr. Salant: That is a complicated question. In studies by Solomon et al. (35), mice injected intraperitoneally with Bence Jones proteins derived from patients with dysproteinemia-related renal diseases reproduced the same patterns of renal disease seen in the patients’ biopsies, including tubular casts resembling myeloma cast nephropathy, basement membrane deposits resembling MIDD, and renal amyloidosis. Some of the Bence Jones proteins obtained from myeloma patients without clinical renal disease failed to produce disease in mice. These findings suggest that the propensity to form different types of renal disease depends on the structure of the individual monoclonal light chains. That study did not address which specific biochemical or physical properties of the individual Bence Jones proteins may govern the pathophysiologic responses observed. Thus, to answer your question directly, it would be necessary to create the Ig modifications described earlier and see whether they induce LCDD when injected into experimental animals.

Dr. Ananth Karumanchi (Assistant Professor of Medicine, Harvard Medical School, Renal Division, Beth Israel Deaconess Medical Center, Boston, MA): I have two questions. First, to Dr. D’Agati: It appears to me that the primary abnormality in this patient is disruption of the endothelial barrier due to subendothelial deposits. Could you comment on the degree of podocyte damage in this patient and whether this could account for the degree of proteinuria seen in this patient? My second question is to Dr. Salant. Could you comment on the physical or biochemical properties of these light chains and/or unidentified heavy chains that would allow preferential affinity toward the glomerular endothelial cells and the subendothelial space?
Dr. D’Agati: In our patient, foot processes were effaced over approximately 75% of the total glomerular capillary surface area. This marked foot process effacement correlates well with the level of nephrotic proteinuria. Although we assume that the
extensive subendothelial deposition of light chains has altered the glomerular sieving barrier, we do not know how light chain deposits, in particular, perturb the glomerular capillary wall’s size and charge dependent permselectivity properties. Dr. Salant: I am not aware of any studies that have directly examined the effect on endothelial cells of the Ig mutations and posttranslational modifications discussed earlier. Most have focused on mesangial cell matrix production and GBM interactions. Nonetheless, it seems quite plausible that endothelial cells might be directly or indirectly affected. Certainly, the endothelial cells were very abnormal in the case described here, although the subendothelial deposits themselves were unusual. Dr. Henry Yager (Chief of Nephrology, Newton Wellesley Hospital, Newton, MA): Has there been any experience with kidney transplantation following high-dose melphalan and stem cell infusion in LCDD?

Dr. Sanchorawala: Our experience with kidney transplantation following HDM/SCT for LCDD is limited to one patient. This patient underwent HDM/SCT and achieved a complete hematologic response. He received a living-unrelated donor renal transplant 2 yr after HDM/SCT. The allograft has functioned well for the past 2 yr.

Acknowledgments
The patient described in this report was enrolled in a clinical trial approved by the institutional review board of the Boston University Medical Center in accordance with federal regulations and the Declaration of Helsinki. We gratefully acknowledge the participation of patients in clinical trials and research at Boston University Medical Center and the assistance of the staff of the Clinical Trials Office and Amyloid Treatment and Research Program. We also thank Dr. Page V. Salenger for access to the pathology specimens, Dr. Page V. Salenger for reviewing the manuscript.

Disclosures
None.

References