

Light Chain Deposition Disease Developing 15 Years Following the Diagnosis of Monoclonal Gammopathy of Undetermined Significance

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Abstract

A 64-year-old woman was admitted because of leg edema. Fifteen years previously she had been diagnosed with monoclonal gammopathy of undetermined significance (MGUS). Urinary immunoelectrophoresis demonstrated positivity for IgA kappa light chains. Bone marrow aspiration revealed a mild plasmacytosis. Her renal biopsy specimen revealed thickened basement membrane, mesangial cell proliferation and an increase in the mesangial matrix. Immunofluorescence studies showed the deposition of kappa light chains in the capillary wall and nodular lesions. These findings confirmed a diagnosis of light chain deposit disease (LCDD) with MGUS. The development of LCDD in patients with MGUS for fifteen years is very rare.

Key words: light chain deposition disease, monoclonal gammopathy of undetermined significance, nephrotic syndrome

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Introduction

Light chain deposition disease (LCDD) is a systemic disease caused by the overproduction and extracellular deposition of a monoclonal immunoglobulin light chain (1). LCDD has been described in patients with lymphoplasma-cytic disorders such as lymphoma, multiple myeloma and Waldenström's macroglobulinemia (2). LCDD preferentially involves cardiac, neural, hepatic or renal tissues and is associated with a variety of clinical manifestations (3). Patients with renal involvement typically have proteinuria with the nephrotic syndrome evident in 30-50% of cases (4).

Monoclonal gammopathy of undetermined significance (MGUS) is a pre-malignant disorder characterized by a clonal plasma cell proliferation in the bone marrow producing a monoclonal paraprotein without end-organ damage. The incidence of MGUS increases with age and is found in approximately 1-5% of the population over 65 years of age (5). Clinical renal disease is uncommon in patients with MGUS. Some patients have mild proteinuria or microscopic

hematuria and only 1% to 2% of patients exhibit mild renal insufficiency due to amyloidosis (6), cryoglobulinemia (7) or monoclonal immunoglobulin deposition disease (8). In this report, we describe a case with monoclonal gammopathy of undetermined significance (MGUS) for fifteen years who developed LCDD.

Case Report

A 64-year-old woman was admitted to our hospital in October 2007 because of leg edema, which had appeared more than six months prior to admission. She had been treated with 50 mg of losartan and 5 mg of amlodipine for hypertension for two years. A diagnosis of MGUS (IgA kappa type) had been made following blood test without bone marrow examination 15 years previously in another clinic. Her oldest blood chemistry data in our hospital showed that her creatinine level was 0.8 mg/dL in September 2003. She has no medical history of diabetes mellitus. Her blood pressure was 120/74 mmHg and pulse rate 72/minute. No crackles and murmurs were detected on chest auscultation and her

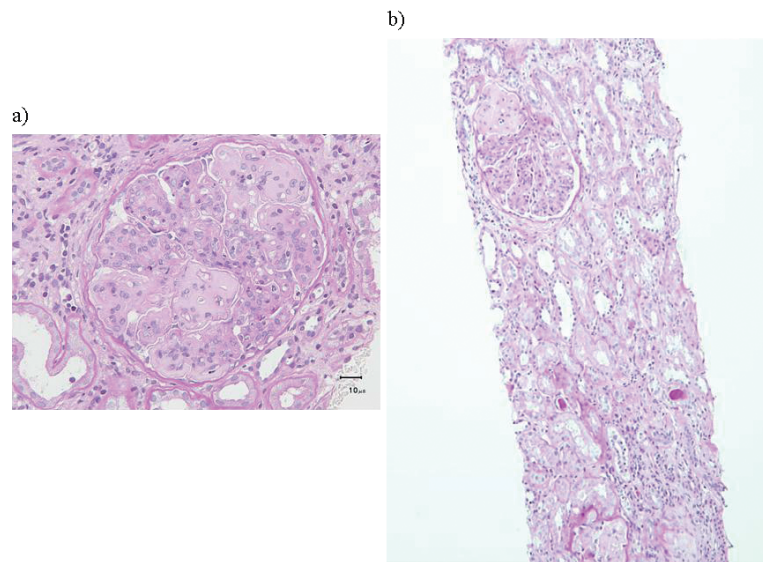


Figure 1. Light microscopy demonstrating mesangial cell proliferation and increased mesangial matrix containing lobular and nodular lesions (a). The tubulointerstitium exhibited lymphocyte infiltration, fibrosis and tubular atrophy (b).

abdomen was non-distended and soft with no hepatosplenomegaly. Severe pretibial edema was noted but no skin lesions were evident. Laboratory investigations demonstrated nephrotic syndrome with marked proteinuria (7.87 g/day), a decreased total serum protein (4.0 g/dL) and albumin (1.8 g/dL) and an increased total cholesterol level (253 mg/dL) despite treatment with 10 mg atorvastatin. No abnormal liver function test was detected. Her electrocardiogram was normal. Abdominal computed tomography did not show hepatosplenomegaly. The serum creatinine was 1.9 mg/dL and the creatinine clearance was 33.3 mL/minute. Microscopic examination of the urine revealed 10 red blood cells/high power field and 8 granular casts/field. Serological studies for antinuclear antibody, cryoglobulins, anti-neutrophil cytoplasmic antibody (ANCA) and antibodies to hepatitis C were negative. The serum levels of IgG, IgA and IgM were 234 mg/dL, 446 mg/dL and 13 mg/dL, respectively. Urinary and serum immunoelectrophoresis was positive for Bence-Jones protein of the IgA kappa type. Bone marrow aspiration test revealed a mild plasmacytosis (8.8% of the total cells). MGUS is characterized by a serum monoclonal protein level of less than 3 g/dL, a proportion of plasma cells in the bone marrow that is less than 10% (9). From this definition and these findings, a diagnosis of MGUS was made.

She underwent a renal biopsy and the specimen revealed twenty-one glomeruli. All glomeruli revealed mesangial cell proliferation and an increase in mesangial matrix that contained lobular and nodular lesions (Fig. 1a). The basement membranes were thickened. The tubulointerstitium exhibited lymphocyte infiltration, fibrosis and tubular atrophy (Fig. 1b). Immunofluorescence studies were negative for IgG, IgA, and IgM but positive for C3 (Fig. 2a) and C1q (Fig. 2b). Strong deposition of kappa light chains was evident in the capillary wall and nodular lesions (Fig. 2c). No kappa light chains depositions were detected in the tubular

basement membrane. Electron microscopy demonstrated fine granular continuous electron dense deposits in the thickened basement membrane (Fig. 3) in the glomeruli but not in the tubules. Congo red stain for amyloid was negative. These findings confirmed a diagnosis of LCDD with MGUS.

Treatment for the LCDD with melphalan (8 mg/day) and prednisolone (60 mg/day) therapy (MP) was initiated. After one course of MP, her creatinine was elevated to 2.9 mg/dL and the MP could not be continued. Treatment with the angiotensin II blocker and Ca channel blocker was continued. At the current time (August 2008) her renal function is stable and her creatinine level is 1.7 mg/dL.

Discussion

Glomerular deposition disease (GDD) in the kidney is often combined with serum paraproteins and hematopoietic disorders in the bone marrow (10). GDD can be divided into three categories in which the deposit is comprised of either fibrillary structures, fine granular structures or crystal structures. The group with a fine granular structure includes non-amyloid monoclonal immunoglobulin deposition diseases such as LCDD, light and heavy chain deposition disease, and heavy chain deposition disease. In 1976, Randall et al were the first to report two patients with terminal renal failure with manifestations of disease developing in multiple organ systems (1). The retention and tissue deposition of light chains produced the organ dysfunction in LCDD. The clinical picture is dominated by renal involvement in essentially all patients, but deposits in the heart, liver and diverse extra-renal sites indicate the systemic nature of LCDD. Pozzi et al reported that the independent risk factor for worse patient survival were age and extrarenal light chain deposition (3). At the presentation of disease, no extra-renal dysfunction was evident in the present case.

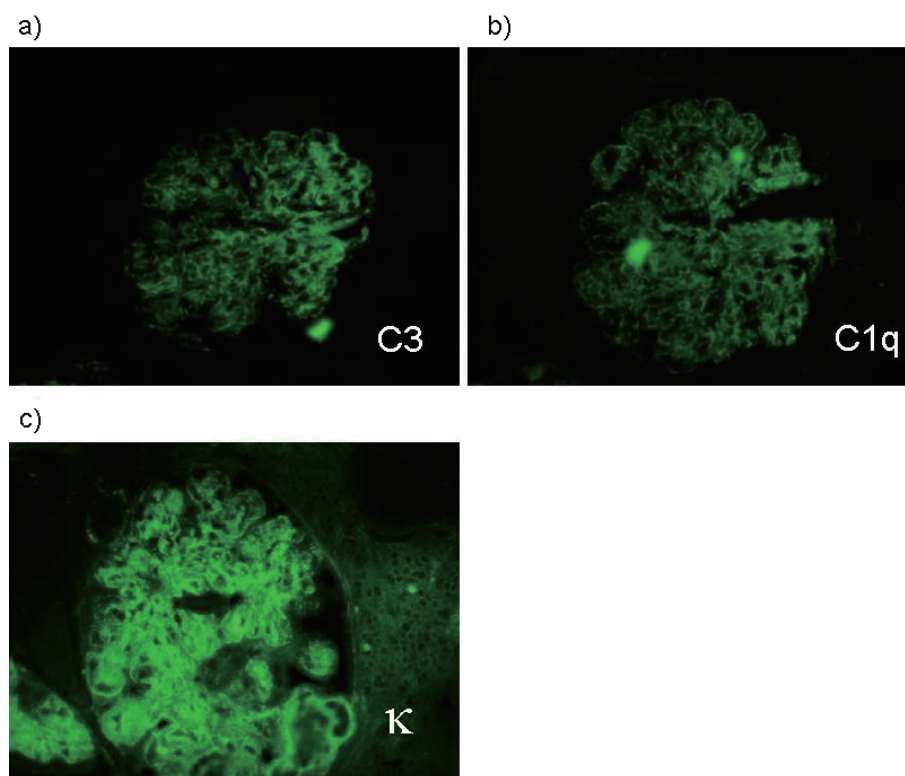


Figure 2. Immunofluorescence microscopy demonstrating that the mesangial, nodular area and capillary wall stained positively for C3 (a), C1q (b), and kappa (c) light chains.

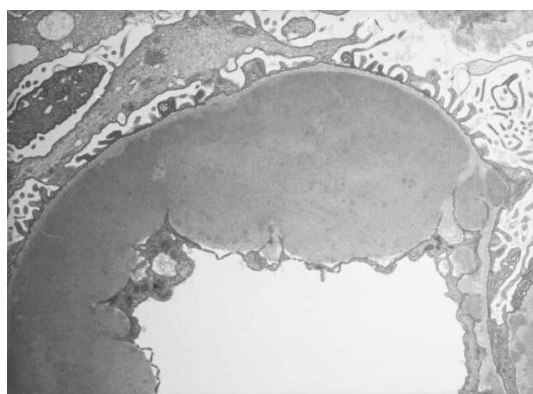


Figure 3. Electron microscopy demonstrating fine granular continuous electron dense deposits in the thickened basement membrane. Original magnification $\times 6,000$.

LCDD is caused by the plasma cell dyscrasias with paraprotein production playing a central pathogenic role. The primary diseases that result in LCDD are mainly multiple myeloma, Waldenström's macroglobulinemia and other lymphoproliferative disorders. MGUS is also reported to be a cause of LCDD. Pauksakon et al reported a series of patients who underwent a renal biopsy and had a monoclonal gammopathy on serum and/or urine electrophoresis and/or had a renal biopsy diagnosis related to paraproteinuria (6). Among 66 patients with paraproteinuria, 14 patients were diagnosed with LCDD. However, in their report, only 5 patients underwent a bone marrow biopsy and only 6 patients were positive for monoclonal protein in serum or urine in

these 14 patients. Thus, the details of patients with LCDD accompanied with MGUS are not available. Pozzi et al reported that LCDD in these patients was caused by multiple myeloma (65%) and lymphoproliferative disorders (3%), with 32% being idiopathic as they did not meet the criteria for the diagnosis of any hematological disease (3). Thus, the exact incidence of LCDD with MGUS is unclear. The present case developed renal insufficiency 15 years following the diagnosis of MGUS. This clinical information is very useful and emphasizes the necessity to carefully follow up patients with MGUS to monitor for complications such as the development of renal disease such as LCDD.

The renal biopsy demonstrated mesangial cell proliferation and increased mesangial matrix forming lobular and nodular lesions. Nodular glomerulosclerosis must be distinguished from other forms of glomerular disease such as diabetes mellitus, membranoproliferative glomerulonephritis and amyloidosis. In the differential diagnosis, immunopathological and electron microscopic analysis is very useful in differentiating between these various diagnoses. In the present case, immunohistochemistry revealed monoclonal kappa light chain deposition in the glomerular basement membrane and mesangial nodules. Furthermore, electron microscopic analysis demonstrated fine granular continuous electron dense deposits in the thickened basement membrane characteristic of LCDD.

Attempts to treat LCDD with MP have been described. Heilman et al reported either stabilization or improvement in renal function after chemotherapy in five of eight LCDD pa-

tients who had a serum creatinine concentration less than 4.0 mg/dL at the initiation of therapy (11). Although MP might be effective for our patient as her creatinine was 1.9

mg/dL, we abandoned the continuation of MP because her renal function worsened after one course of MP.

References

1. Randall RE, Williamson WC Jr, Mullinax F, Tung MY, Still WJ. Manifestations of systemic light chain deposition. *Am J Med* **60**: 293-299, 1976.
2. Tubbs RR, Gephardt GN, McMahon JT, Hall PM, Valenzuela R, Vidt DG. Light chain nephropathy. *Am J Med* **71**: 263-269, 1981.
3. Pozzi C, D'Amico M, Fogazzi GB, et al. Light chain deposition disease with renal involvement: clinical characteristics and prognostic factors. *Am J Kidney Dis* **42**: 1154-1163, 2003.
4. Buxbaum JN, Chuba JV, Hellman GC, Solomon A, Gallo GR. Monoclonal immunoglobulin deposition disease: light chain and light and heavy chain deposition diseases and their relation to light chain amyloidosis. Clinical features, immunopathology, and molecular analysis. *Ann Intern Med* **112**: 455-464, 1990.
5. Kyle RA. Monoclonal gammopathy of undetermined significance. *Blood Rev* **8**: 135-141, 1994.
6. Paueksakon P, Revelo MP, Horn RG, Shappell S, Fogo AB. Monoclonal gammopathy: significance and possible causality in renal disease. *Am J Kidney Dis* **42**: 87-95, 2003.
7. Brouet JC, Clauvel JP, Danon F, Klein M, Seligmann M. Biologic and clinical significance of cryoglobulins. A report of 86 cases. *Am J Med* **57**: 775-788, 1974.
8. Jensen H, Wiik A. Monoclonal immunoglobulinaemia associated with glomerulopathy. *Acta Med Scand* **197**: 265-269, 1975.
9. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* **356**: 2582-2590, 2007.
10. Joh K. Pathology of glomerular deposition diseases. *Pathol Int* **57**: 551-565, 2007.
11. Heilman RL, Velosa JA, Holley KE, Offord KP, Kyle RA. Long-term follow-up and response to chemotherapy in patients with light-chain deposition disease. *Am J Kidney Dis* **20**: 34-41, 1992.