

## Case Report

# Renal amyloidosis complicated by light chain deposition nephropathy: a case report

Xiaoyang Yu, Ping Lan, Jie Feng, Xueliang Feng, Liyi Xie

*Department of Nephrology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China*

Received March 10, 2019; Accepted March 27, 2019; Epub June 1, 2019; Published June 15, 2019

**Abstract:** Light chain amyloidosis (AL) and light chain deposition disease (LCDD) are systemic diseases caused by an abnormal production of monoclonal immunoglobulin light chains and their deposition in systemic tissue. We herein present a rare case of renal amyloidosis complicated with light chain deposition nephropathy. The patient presented with nephrotic syndrome and an increased serum creatinine. Laboratory studies showed the serum  $\kappa$  light chain was decreased and the urine free  $\lambda$  light chain was positive. On a lighted microscopy examination of the renal cortical tissue,  $\lambda$  and  $\kappa$  light chain protein deposits were in the glomerular and renal tubular basement membranes and Congo red staining was positive. It was determined using electron microscopy that amyloid fibrils and continuous electron-dense granules were deposited in the glomerular basement membrane. Due to differences in the protein polymerization mechanisms, it is almost impossible for AL and LCDD to coexist. This rare case can help provide ideas for clinical diagnosis and for exploring new therapeutic targets.

**Keywords:** Renal amyloidosis, light chain deposition, monoclonal immunoglobulin

## Introduction

Light chain amyloidosis (AL) and light chain deposition disease (LCDD), most often secondary to lymphoproliferative disorders, are systemic diseases caused by an abnormal production of monoclonal immunoglobulin light chains and their deposition in systemic tissue. The monoclonal light chains are small enough to be freely filtered by the kidneys and become Bence-Jones protein. Light chain deposition nephropathy is characterized by the deposition of monoclonal immunoglobulin light chains in the form of non-immune complexes in the glomerular mesangial region and the basement membrane. About 18% of multiple myeloma patients have light chain disease [1]. Immunoglobulin light chain amyloidosis is a kind of plasma cell disease whose amyloid protein is derived from immunoglobulin light chain or light chain fragments produced by monoclonal proliferating plasma cells in bone marrow [2]. Renal amyloidosis accounts for about 0.21%-1.00% of all renal biopsies [3]; however, the survival time is not more than 3 years if left untreated [4]. Due to different disease charac-

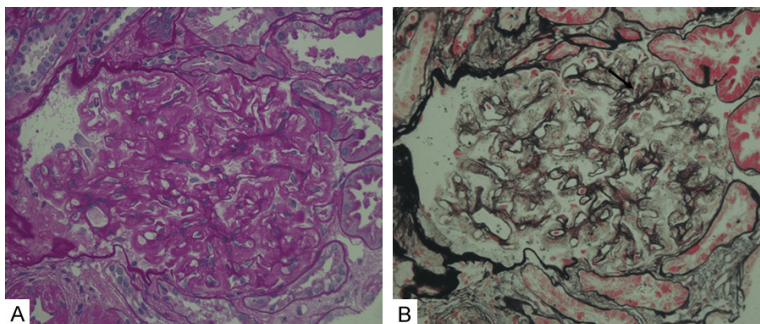
teristics, it is unlikely that renal amyloidosis is complicated with LCDD in the same individual. The concurrence in this case needs an investigation of the pathogenesis, and we aim to provide ideas for clinical diagnosis and exploring new therapeutic targets.

## Case report

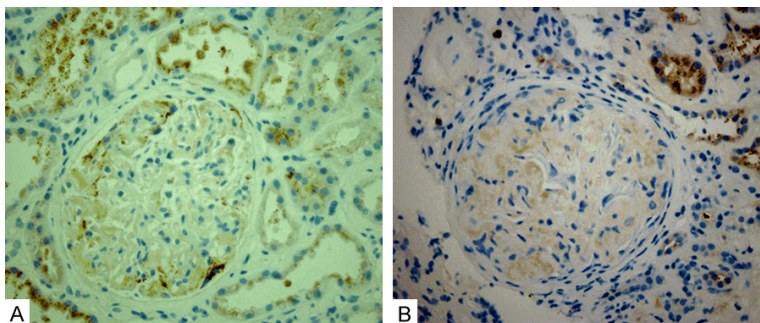
A 57-year-old Chinese male presented with complaints of intermittent edema of double lower limbs associated with proteinuria for more than 3 years. His urine volume was about 400 ml/day and diuretic therapy had not been effective. He denied rash and joint pain and had no history of hypertension or diabetes.

A routine blood examination showed the WBC count  $7.79 \times 10^9/L$ , the platelet count  $215 \times 10^9/L$ , and the hemoglobin 85 g/L. The urinary protein was 3.82 g/24 h. Other indices of biochemistry showed BUN 19.24 mmol/L (3.1-8.0 mmol/L), creatinine 103  $\mu\text{mol/L}$  (57-97  $\mu\text{mol/L}$ ) and albumin 17.7 g/L (40-55 g/L). His serum protein electrophoresis showed as  $\gamma$  globulin 6.4% (11.1-18.8%), M protein negative,  $\kappa$  light

## Renal amyloidosis complicated by LCDD



**Figure 1.** Light microscopy characteristics of kidney tissue. A. Amorphous acellular and pale eosinophilic material deposits in the glomerular basement membrane and the mesangial region. The mesangial matrix is proliferated. (PAS staining  $\times 400$ ). B. Eyelash-like projections of glomerular basement membrane ( $\uparrow$ ) (PASM staining  $\times 400$ ).



**Figure 2.** Immunohistochemical characteristics of kidney tissue. A.  $\kappa$  light chain proteins deposits in the glomerular and renal tubular basement membranes ( $\kappa$  light chain staining  $\times 400$ ). B.  $\lambda$  light chain proteins deposits in the glomerular and tubular basement membrane and mesangium ( $\lambda$  light chain staining  $\times 400$ ).

chain 0.66 g/L (1.7-3.7 g/L), and  $\lambda$  light chain 1.47 g/L (0.9-2.1 g/L). Detection of urine Bence-Jones protein showed the free  $\lambda$  light chain was positive. ANCA, autoantibodies, including the PLA2R antibody and the hepatitis virus were negative. A chest X-ray showed no obvious abnormality.

### Renal biopsy findings

The specimen for the light microscopy contained 7 glomeruli, 2 of which were globally sclerotic. There was amorphous, acellular, pale eosinophilic material in the mesangium and extending out to glomerular capillary walls according to periodic acid-Schiff (PAS) staining (**Figure 1A**). Segmental eyelash-like projections could be seen using periodic acid-sliver methenamine (PASM) staining (**Figure 1B**). The renal tubular epithelial cells had vacuoles and granular degeneration. The tubular lumina contained protein casts, and the interstitium was infiltrat-

ed with lymphocytes and monocytes. The small arterial walls were thickened, in which amorphous acellular and pale eosinophilic material was deposited. Immunofluorescence showed deposits of IgG, IgA, and IgM in the mesangial region. Immunohistochemical staining showed the  $\lambda$  and  $\kappa$  light chain deposits were in the glomerular and renal tubular basement membranes and the mesangium (**Figure 2A, 2B**). In addition, Congo red and oxidized Congo red staining were positive (**Figure 3**).

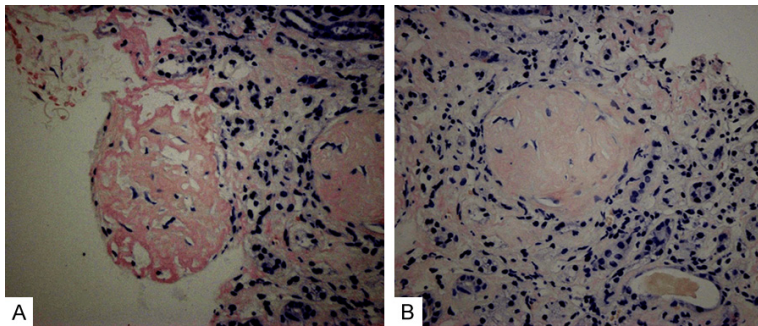
Electron microscopy demonstrated that non-branch amyloid fibrils were deposited in the glomerular basement membrane (GBM) and the mesangial region replacing normal structures (**Figure 4C, 4D**). The fiber diameter was from 7.7 nm to 13.61 nm. There were continuous punctate deposits in the inner layer of the GBM (**Figure 4A, 4B**).

### Discussion

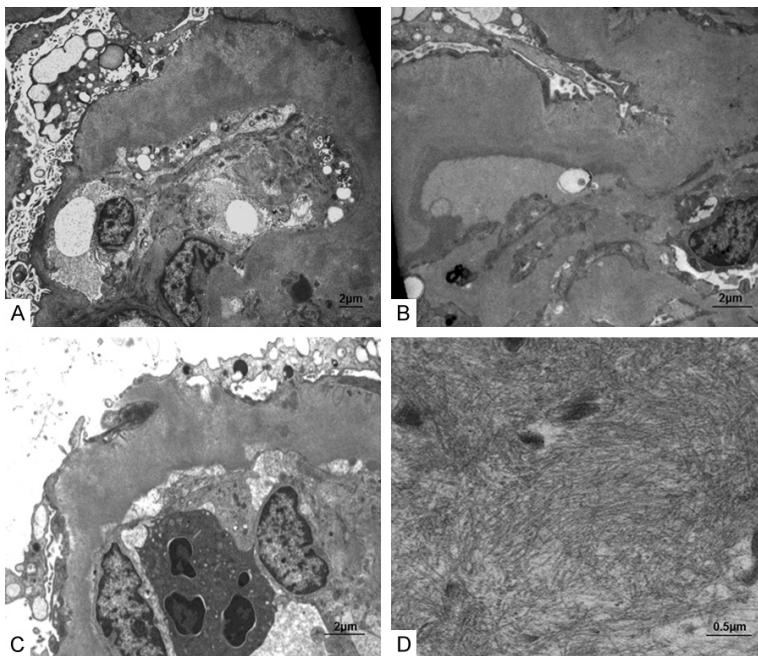
AL and LCDD both belong to plasma cell tumors, also known as monoclonal immunoglobulin deposition disease (MIDD). LCDD constitutes the most common form of MIDD (75-80%) [5]. AL and LCDD typically occur in association with multiple myeloma (MM) or other lymphoplasma-cytic disorders. The kidney is the most common involved organ, often being led to progressive renal failure [6]. LCDD is characterized by the deposition of monoclonal immunoglobulin light chains in the form of non-immune complexes in the glomerular mesangial region and the basement membrane. In AL, the abnormal light chain (amyloid precursor) is transformed into a  $\beta$ -pleated sheet structure, which is responsible for the morphologic, optical, and tinctorial properties of amyloid.

The patient in this case suffered from severe proteinuria accompanied by renal insufficiency, and his urine free  $\lambda$  light chain was positive. The decrease of serum  $\kappa$  light chain may be related

## Renal amyloidosis complicated by LCDD



**Figure 3.** Congo red staining shows amyloid protein formation. (A and B) The glomerulus is infiltrated by homogeneous acellular material replacing normal structures (A: Congo red staining  $\times 400$ , B: Oxidized Congo red staining  $\times 400$ ).



**Figure 4.** Electron microscopic characteristics of kidney tissue. (A and B) The GBM is thickened. Continuous punctate deposits are in the inner layer of GBM (A:  $\times 4000$ , B:  $\times 6000$ ). (C and D) The disordered and non-branch amyloid fibril deposits in the GBM, the diameter of which is from 7.7 nm to 13.61 nm. (C:  $\times 6000$ , D:  $\times 30000$ ).

to the deposition of the light chain in renal tissue. Immunohistochemical staining showed the  $\lambda$  light chain deposited in the GBM and mesangium and the glomerular Congo red staining was positive. Amyloid fibrils were observed by electron microscopy. The  $\kappa$  light chain was deposited in the glomerular and renal tubular basement membranes. It demonstrated continuous punctate deposits in the inner layer of the GBM, which is consistent with an LCDD diagnosis. Therefore, the pathological

diagnosis was AL complicated with LCDD. Due to the differences in the protein polymerization mechanisms, it is almost impossible for AL and LCDD to coexist. One possible etiology is that the patient had biclonal plasma cell tumors, and each produces different types of free light chains and causes different types of immunoglobulin deposition. It also may be related to the biochemical environment of the local tissues, which induce different pathological processes in the same individual through different signal transduction pathways, which mediates the same structural antigenicity forming different aggregation patterns.

The occurrence of MIDD is associated with the deposition of the immunoglobulin light chain. Different light chain types may have different pathogenicities due to their physicochemical properties. LCDD is mainly  $\kappa$  light chain deposition, but  $\lambda$  light chain deposition presents severe renal tubular lesions [7]. AL- $\kappa$  is more likely to deposit in the liver and vascular walls, while AL- $\lambda$  has a visible characteristic of causing amyloidosis, more likely to deposit in the glomeruli [8, 9].

The different pathological forms of LCDD and AL may be related to the structural changes

of light chain proteins, the process of protein aggregation and dissolution, and the biochemical environment of the local tissues. For instance, point mutation in the gene coding for light chain amino acid sequences leads to the substitution of a single amino acid, which may affect the stability of the protein structure, resulting in the abnormal deposition of light chain proteins [10, 11]. Amino acid Asp82 replaced by Ile is the most common mutation in LCDD, which can change the structure of the

light chain and the morphology after its aggregation and deposition. AL-associated amino acid Arg61 in the light chain variable region is converted to Asn, resulting in a decline in the stability of the protein structure, and influencing the protein tertiary structure and its folding frizzy state, makes it easy to form a  $\beta$ -pleated sheet structure [12]. Helms and co-workers proposed that the importance of Arg61 for stability may be due to its role in making a key electrolytic bridge with Asp82 located on an adjacent loop [12]. Russell's team proved that different light chain proteins deposited in LCDD and AL through their interaction with mesangial cells can activate different signaling pathways, controlling mitogenic activities and abnormal cytokine production, and stimulate the different reactions of the extracellular matrix, which leads to different pathological processes [13]. The light chain in LCDD, for instance, mediated by TGF- $\beta$ , PDGF-B, stimulates hyperplasia of the extracellular matrix, such as type IV collagen, laminin, fibronectin, and tenascin, leading to nodular hyperplasia sclerosis of the mesangial region.

Treatment options for AL complicated with LCDD include bortezomib, thalidomide, and cyclophosphamide plus dexamethasone. Also, the combined use of autologous hematopoietic stem cell transplantation improves the hematology remission rate of MIDD. But in recent years, the prevalence of MIDD has increased, mostly among elderly patients and accompanied by many basic diseases. In the early stages of LCDD, the clinical manifestations are nephrotic syndrome with normal or mild renal impairment, and the pathological findings show a segmental deposition of the light chains in glomeruli. In the disease's later period, in addition to the extensive deposition of GBMs, renal tubular basement membranes (TBM) and small vascular walls, the light chains are also seen in other organs, and renal function is seriously damaged. Sayed and co-workers reported that about 62% of patients require renal replacement therapy, and 36% of patients died of infection, ischemic cardiomyopathy, cerebrovascular accident, gastrointestinal bleeding, multiple myeloma, and so on [14]. Similarly, in the early stages, AL showed segmental amyloid fiber distribution in the glomerular mesangial areas and the basement membranes, with moderate proteinuria and normal renal func-

tion. With the progress of the disease, the deposition of amyloid proteins are gradually increased, and renal hypofunction transitions to nephrosis in the terminal stage. Therefore, it is very important to diagnose and optimize the treatment regimens as early as possible, especially for the patients with these two concurrent diseases. The deposition of monoclonal immunoglobulin light chains may lead to AL, non-amyloid LCDD or a concurrence of the two. The specific pathogenesis is unclear, so it needs to be further explored in the future.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Liyi Xie, Department of Nephrology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi, China. Tel: +86-13700282059; Fax: +86-21-64085875; E-mail: xieliyi0313@163.com

### References

- [1] Mahto M, Mohapatra S, Sumitra G, Kaushik S, Mishra TK, Saxena A. A case of light chain deposition disease (LCDD) in a young patient. *Indian J Clin Biochem* 2011; 26: 420-422.
- [2] Gertz MA, Lacy MQ, Dispenzieri A. Immunoglobulin light chain amyloidosis and the kidney. *Kidney Int* 2002; 61: 1-9.
- [3] Pepys MB. Pathogenesis, diagnosis and treatment of systemic amyloidosis. *Philos Trans R Soc Lond Biol Sci* 2001; 356: 203-210.
- [4] Gatt ME, Palladini G. Light chain amyloidosis 2012: a new era. *Br J Haematol* 2013; 160: 582-598.
- [5] Said S, J Cooper C, C Nwosu A, E Bilbao J, T Hernandez G. Hypertension, renal failure, and edema in a 38-year-old man: light chain deposition disease; a case report and review of the literature. *J Nephropathol* 2014; 3: 63-68.
- [6] Gallo G, Picken M, Buxbaum J, Frangione B. The spectrum of monoclonal immunoglobulin deposition disease associated with immunocytic dyscrasias. *Semi Hematol* 1989; 26: 234-245.
- [7] Picken MM, Shen S. Immunoglobulin light chains and the kidney: an overview. *Ultrastruct Pathol* 1994; 18: 105-112.
- [8] Eirin A, Irazabal MV, Gertz MA, Dispenzieri A, Lacy MQ, Kumar S, Sethi S, Nasr SH, Cornell LD, Fidler ME, Fervenza FC, Leung N. Clinical features of patients with immunoglobulin light chain amyloidosis (AL) with vascular-limited deposition in the kidney. *Nephrol Dial Transplant* 2012; 27: 1097-1101.

## Renal amyloidosis complicated by LCDD

- [9] Basnayake K, Stringer SJ, Hutchison CA, Cockwell P. The biology of immunoglobulin free light chains and kidney injury. *Kidney Int* 2011; 79: 1289-1301.
- [10] Ronco PM, Alyanakian MA, Mougnot B, Aucouturier P. Light chain deposition disease: a model of glomerulosclerosis defined at the molecular level. *J Am Soc Nephrol* 2001; 12: 1558-1565.
- [11] Buxbaum JN. Abnormal immunoglobulin synthesis in monoclonal immunoglobulin light chain and light and heavy chain deposition disease. *Amyloid* 2001; 8: 84-93.
- [12] Helms LR, Wetzel R. Specificity of abnormal assembly in immunoglobulin light chain deposition disease and amyloidosis. *J Mol Biol* 1996; 257: 77-86.
- [13] Russell WJ, Cardelli J, Harris E, Baier RJ, Herrera GA. Monoclonal light chain-mesangial cell interactions: early signaling events and subsequent pathologic effects. *Lab Invest* 2001; 81: 689-703.
- [14] Sayed RH, Wechalekar AD, Gilbertson JA, Bass P, Mahmood S, Sachchithanatham S, Fontana M, Patel K, Whelan CJ, Lachmann HJ, Hawkins PN, Gillmore JD. Natural history and outcome of light chain deposition disease. *Blood* 2015; 126: 2805-2810.