

## Five Sequential Evaluations of Renal Histology in a Patient with Light Chain Deposition Disease

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### Abstract

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A 58-year-old man was referred to our institution for an evaluation of nephrotic range proteinuria. Renal biopsy showed a marked expansion of the mesangial matrix and thickening of glomerular basement membrane (GBM) in periodic acid-silver methenamine (PAM). Immunofluorescence (IF) revealed strong staining for the monoclonal kappa light chain. EM demonstrated massive subendothelial and mesangial dense deposits. As a result, light chain deposition disease (LCDD) was diagnosed. Melphalan and prednisolone (MP) therapy was started, which was continued for 10 years with minimal complications. Serial evaluations of renal histology revealed the resolution of nodular lesions and the glomeruli became nearly normal. MP therapy can therefore be an effective therapeutic option for LCDD if it is continued over the long term.

**Key words:** light chain deposition disease, renal histology, melphalan and prednisolone therapy

(Intern Med 55: 2993-2999, 2016)

(DOI: 10.2169/internalmedicine.55.6213)

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### Introduction

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Light chain deposition disease (LCDD) is a life-threatening condition that often results in progressive renal dysfunction with a fatal outcome. It features the deposition of monoclonal kappa (or rarely lambda) light chains in various organs, including the kidneys (1). Renal involvement is found in up to 96% of patients with LCDD, and it was reported that end-stage renal failure occurs in 60% at 1 year, with proteinuria >1 g/day in 84% and nephrotic range proteinuria in 40% that is characteristically accompanied by microscopic hematuria (2, 3). It was also reported that the median time for LCDD to progress to uremia was 2.7 years, with a renal survival rate of 67% at 6 months, 62% at 1 year, 54% at 2 years, 43% at 3 years, 40% at 4 years, and 31% at 8 years (2).

Some of the newer therapeutic options for multiple myeloma, such as bortezomib or peripheral blood stem cell transplantation combined with high-dose chemotherapy, have

been applied to LCDD associated with multiple myeloma, and have been reported to stabilize the renal function and improve renal survival (1, 4, 5). However, the optimum treatment for LCDD has not been completely established (1).

In patients who have LCDD associated with multiple myeloma, Gokden et al. reported that light microscopy (LM) reveals a wide array of histological changes. Nodular glomerulosclerosis has been considered the most common feature of LCDD, but they found that it was only present in 30% of the cases and an increase of the mesangial matrix was observed in 23% (6).

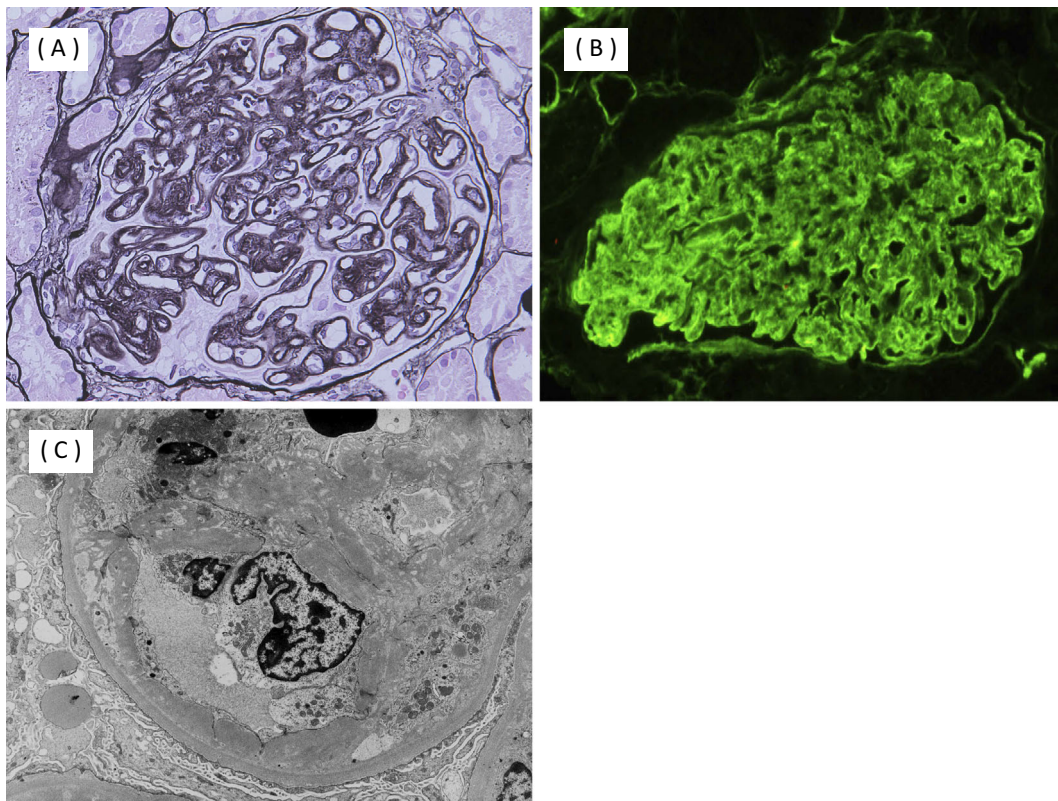
We herein present the findings of a 58-year-old Japanese man in whom primary kappa chain LCDD was diagnosed by an investigation of nephrotic range proteinuria and renal dysfunction. In this patient, a sequential renal histological evaluation was performed five times by LM, immunofluorescence (IF), and EM. The findings showed that long-term clinical remission due to treatment with melphalan and prednisolone (MP therapy) was associated with histological re-

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Received for publication July 23, 2015; Accepted for publication November 23, 2015

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**Figure 1.** Light microscopy of the first renal biopsy specimen revealed rare global glomerular sclerosis and tubulointerstitial fibrosis. (A) periodic acid-silver methenamine (PAM) staining shows massive mesangial expansion with the accumulation of the mesangial matrix and a double contour of the glomerular basement membrane (GBM). (B) Immunofluorescence for the kappa light chain. This glomerulus shows mesangial and peripheral (presumably subendothelial) kappa light chain deposits. Light chain deposition is also observed along the tubular basement membrane adjacent to the glomerulus. (C) At the first renal biopsy, electron microscopy (EM) showed a prominent mesangial matrix accumulation and subendothelial dense deposits.

mission and the regression of nodular lesions. We also discuss the pathogenesis of primary LCDD.

### Case Report

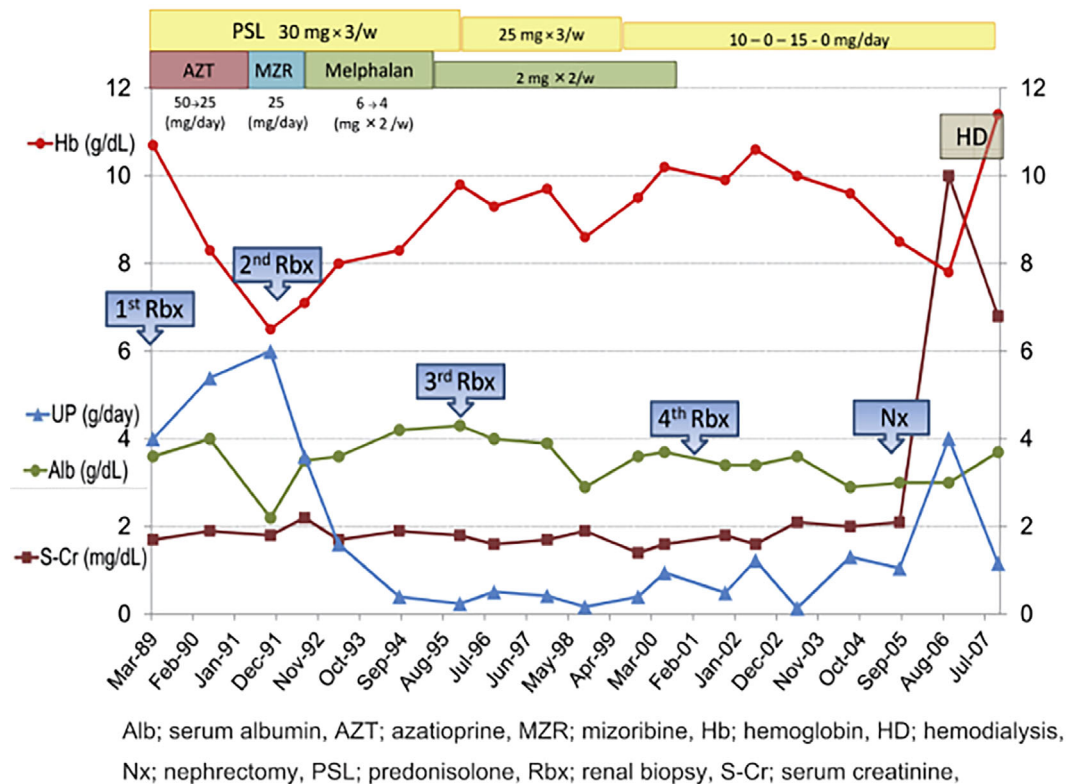
A 58-year-old man was referred to our hospital in January 1989 for an evaluation of weight gain, nephrotic range proteinuria, and renal dysfunction. He had no relevant medical history. On examination, he had a temperature of 36.5°C, a pulse rate of 76/min, a respiration rate of 14/min, and a blood pressure of 170/100 mmHg. Pitting edema of the lower extremities was noted bilaterally.

Laboratory findings were as follows: serum albumin was 2.9 g/dL, total protein was 5.0 g/dL, urea nitrogen was 27 mg/dL, and the serum creatinine was 1.8 mg/dL [(estimated glomerular filtration rate (eGFR) was 32 mL/min]. Antinuclear antibody was negative. Serum C3 was 50 mg/dL, C4 was 32 mg/dL, and CH50 was 34 U/mL. The serum level of immunoglobulin G (IgG) was 669 mg/dL, with an IgA level of 122 mg/dL and IgM level of 87 mg/dL, and there was no monoclonality. The serum monoclonal protein and urinary Bence Jones protein (using electrophoresis method) were negative. Urinary protein excretion was 4.2 g daily, and the

sediment contained 1 to 5 erythrocytes per high-power field. Although bone marrow aspiration showed a slight increase of mature plasma cells, even showing positivity for kappa and lambda (4.2% of nucleated cells), there were no abnormal findings on the smear and no osteolytic lesions were identified by a full skeletal survey. Therefore, he did not meet the criteria for multiple myeloma or monoclonal gammopathy of undetermined significance.

#### First renal biopsy

Renal biopsy was performed in January 1989 and LM revealed global sclerosis in 2/25 glomeruli. Mild to moderate expansion of the mesangial matrix and marked thickening of the glomerular basement membrane (GBM) with a double contour were noted evenly on almost all non-sclerotic glomeruli in sections with periodic acid-Schiff (PAS) and periodic acid-silver methenamine (PAM) staining (Fig. 1A). Congo red staining was negative. Immunofluorescence microscopy (IF) showed strong staining for kappa light chain in the mesangial region and along the GBM, but weakly and partially along the tubular basement membrane (TBM) (Fig. 1B). There was no staining for lambda light chain, IgG, IgA, and IgM. Electron microscopy (EM) revealed



**Figure 2.** Clinical course.

massive subendothelial dense deposits and edema of the GBM and dense deposits on inner zone of TBM, as well as mesangial dense deposits (Fig. 1C). No microfibrillar structures were observed. Atrophy of the tubules and fibrosis of the interstitial space were minute. Sclerotic change of small arteries was mild. These clinical and histological features confirmed the diagnosis of kappa-type LCDD.

#### Clinical course (Fig. 2)

Treatment was started with prednisolone (30 mg, 3 times weekly) and azathioprine (50 mg daily) was added in 1989. Azathioprine was replaced by breedinine (25 mg daily) within two years because of progressive anemia (hemoglobin 6.2 g/dL), but his proteinuria increased to 5.8 g daily. In 1991, melphalan was started at a dose of 6 mg administered 2 days per week together with prednisolone [methylprednisolone (MP) therapy]. The dose of melphalan was soon tapered to 4 mg, and it was later reduced to 2 mg in 1995, after which it was discontinued in 2001. Prednisolone was decreased to 25 mg 3 times weekly in 1996, and was tapered to a cycle of 10 mg-0 mg-15 mg-0 mg in 1999. His proteinuria gradually improved and remained at a level of 0.5 to 1.5 g per day until 2005. The serum monoclonal protein and urinary Bence Jones protein remained negative over time. Serum creatinine also remained around 1.5 to 2 mg/dL. In 2005, right nephrectomy was performed because of renal cell carcinoma, after which his creatinine deteriorated to 3.5 mg/dL and hemodialysis was started 1 year later because of over-filtration for the remnant kidney.

Antihypertensive agents such as calcium antagonist and

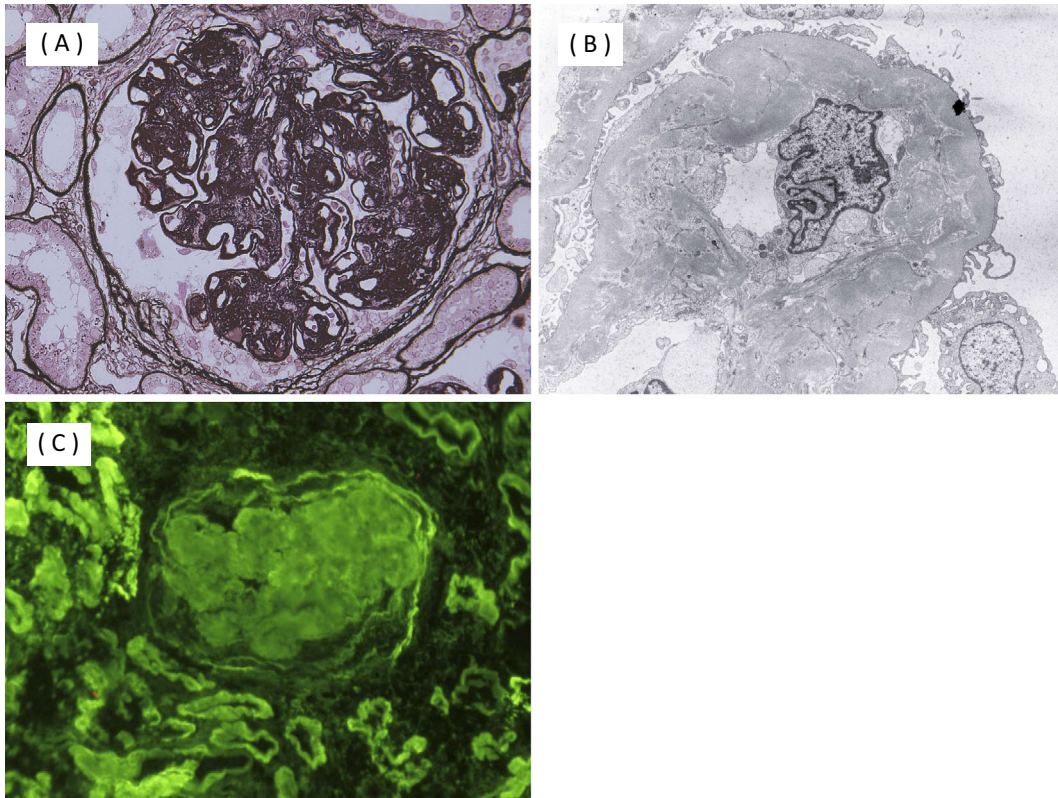
angiotensin converting enzyme inhibitors were administered to treat hypertension until the initiation of hemodialysis after his first admission. Until 2007, no serum monoclonal protein or urinary Bence Jones protein (using electrophoresis method) were detected, though a significant elevation of the serum kappa light chain was detected in comparison to that of the lambda chain, while the free light chain in the serum and urine was not considered to be applicable.

#### Sequential renal histology

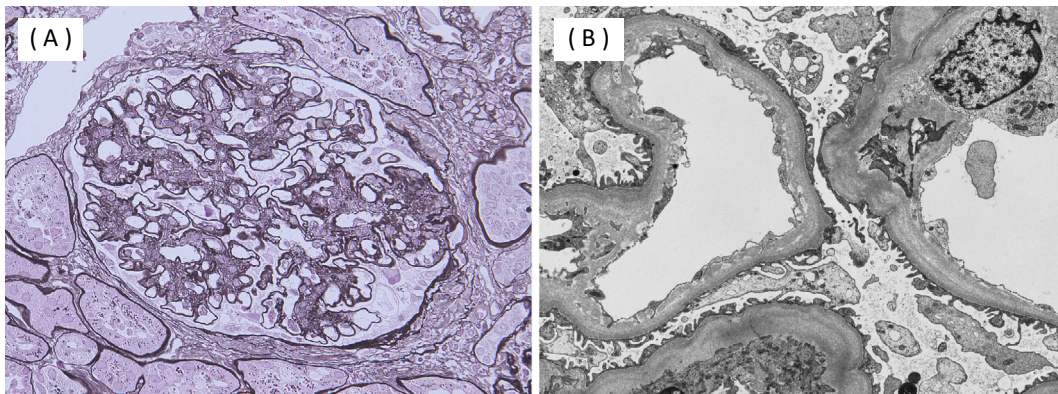
Sequential renal biopsies were performed in 1989 (1st), in 1991 (2nd) (at Cre of 2.0 mg/dL), in 1995 (3rd) (at Cre of 1.8 mg/dL), in 2001 (4th) (at Cre of 1.8 mg/dL), and surgical nephrectomy was done in 2005 (5th) (at Cre of 2.4 mg/dL).

The second renal biopsy (1991) was performed because of an exacerbation of this disease and therapeutic reexamination. LM containing 22 glomeruli did not show any global sclerosis, but multiple marked nodules were observed which had formed due to the expansion of mesangial and subendothelial lesions (Fig. 3A), while EM showed an increase of the mesangial and subendothelial dense deposits of GBM and thickening of TBM (Fig. 3B), and IF showed strong staining for the kappa light chain along TBM in addition to glomeruli (Fig. 3C). Tubulointerstitium and the small arteries showed findings similar to the LM findings identified at the 1st biopsy.

The third renal biopsy (1995) was done to check the time of tapering of MP therapy. LM revealed global sclerosis in 68/82 glomeruli. Atrophy of tubules and fibrosis with in-



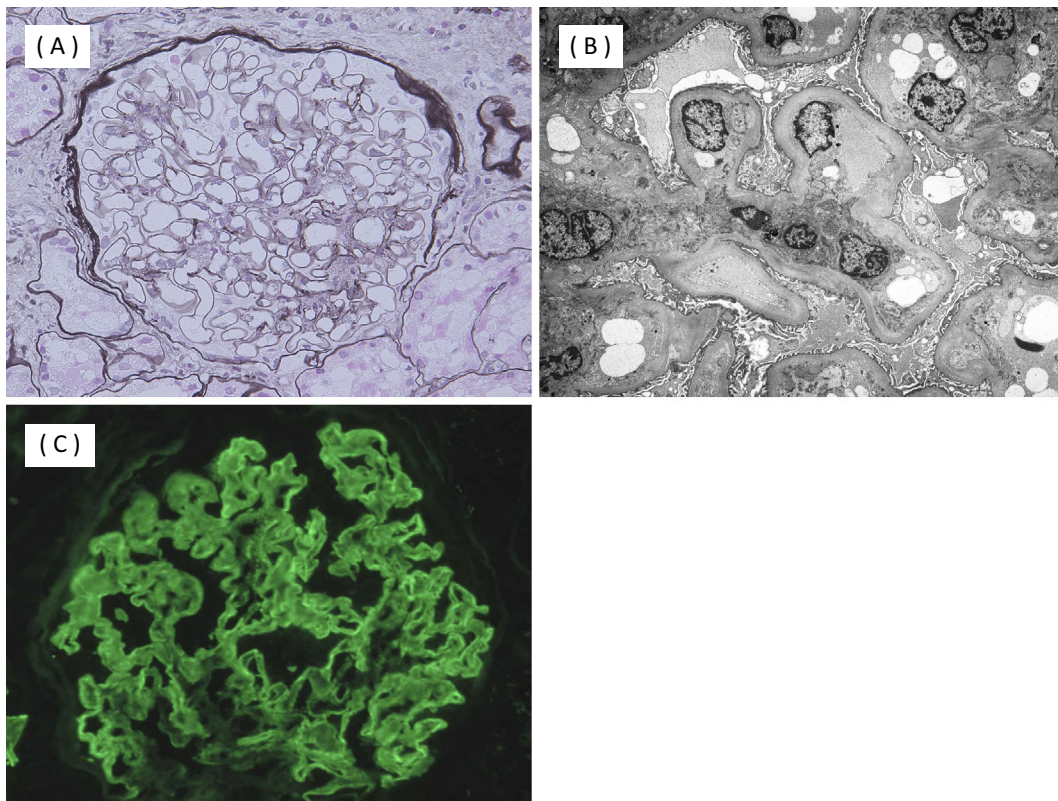
**Figure 3.** Light microscopy of the second renal biopsy revealed no global glomerular sclerosis. Interstitial fibrosis and tubular atrophy were observed in 10% of the renal cortex. (A) A PAM-stained section from the second biopsy reveals marked mesangial expansion associated with glomerular lobulation and typical mesangial nodular lesions. (B) EM shows severe thickening of the GBM with dense subendothelial/mesangial deposits and mesangial interposition. (C) IF showed strong staining for the kappa light chain also along the TBM in addition to the glomeruli.



**Figure 4.** Light microscopy of the third renal biopsy revealed significant chronic ischemic change due to long-term systemic hypertension. Only 14 of 82 glomeruli were preserved and all other glomeruli showed segmental or global sclerosis. Interstitial fibrosis and tubular atrophy involved about 50% of the renal cortex and moderate arteriosclerosis with intimal hyalinosis. (A) A PAM-stained section from the third biopsy shows a marked reduction of nodular lesions. The remnant glomerulus displays slight mesangial expansion with an accumulation of the matrix. (B) EM reveals that mesangial, subendothelial, and intramembranous deposits have become electron-lucent and the GBM is thinner than in the earlier biopsy specimens.

flammation of interstitial space became definite around glomeruli with global sclerosis, and small arteries became sclerotic and hyalinotic. Each of the non-sclerotic 14

glomeruli demonstrated a marked reduction of the mesangial nodules and thinning of the GBM (Fig. 4A). EM also revealed a marked reduction of the subendothelial lesions of



**Figure 5.** Light microscopy of the fourth renal biopsy, 26 of 34 glomeruli showed global sclerosis. Interstitial fibrosis and tubular atrophy involved about 70% of the renal cortex and severe arteriosclerosis. (A) A PAM-stained section from the fourth biopsy showed that the glomerulus is almost normal in appearance. (B) EM also demonstrates normal glomerular architecture with normalization of the mesangial area without excess matrix accumulation, and normal thickness of GBM, consistent with the LM findings. (C) Immunofluorescence for the kappa light chain in the fourth biopsy specimen. Despite the improvement in the light microscopic findings, kappa light chain deposits still exist.

GBM, mesangial lesions and inner zone lesion of GBM, with an appearance of new electron-lucent areas (Fig. 4B).

A fourth renal biopsy (2001) was done to check the time of further tapering of MP therapy. LM showed global sclerosis in 26/34 glomeruli. The changes in the tubulointerstitium and small arteries were similar to those observed after the 3rd biopsy. Each of non-sclerotic 8 glomeruli revealed a complete resolution of the nodular lesions, and had a nearly normal appearance by LM (Fig. 5A) as well as EM (Fig. 5B). However, strong staining for kappa light chain was still detected along the GBM, although the staining of the kappa light chain along TBM had become obscure (Fig. 5C).

A surgical specimen of the resected kidney (2005) showed sclerotic regions in the glomeruli, moderate to severe tubular atrophy, and fibrosis of the tubulointerstitium was clearly distinguished and it was separate from the nearly normal region, and it occupied approximately 80% of the total renal cortical region, which was similar to the LM and IF findings observed in the fourth biopsy, which was considered to probably be due to long-term hypertension and oral steroid therapy, and hypertensive ischemia of the small renal arteries. Moreover, his sequential renal histology also showed a deterioration of chronic renal damage with

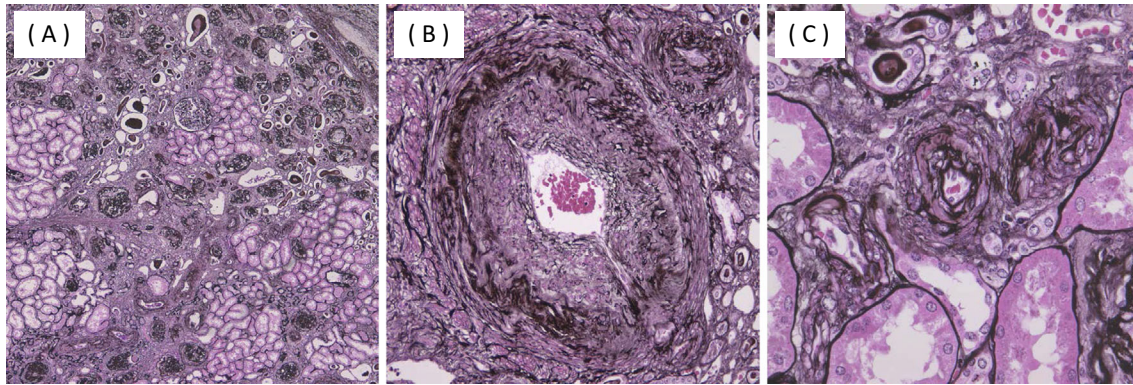
the development of arterio-sclerotic changes associated with long-term systemic hypertension. The accumulation of the meningeal matrix and thickening of the GBM on non-sclerotic glomeruli had both slightly increased (Fig. 6), presumably because of the termination of the MP therapy.

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## Discussion

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MP therapy is one of the classical chemotherapy regimens for multiple myeloma and it has also been used for LCDD. However, myelosuppression due to melphalan means that long-term continuation of this therapy is not feasible. Previously, only three cases achieved histological remission (7-9). Komatsuda et al. reported a 64-year-old man with kappa-type LCDD due to multiple myeloma who received MEVP therapy (melphalan, cyclophosphamide, vincristine, and prednisolone). A second renal biopsy after 6 years showed a marked reduction of nodular lesions and the disappearance of kappa light chain deposits, and monoclonal kappa light chain protein became undetectable in his urine and serum (7). Hotta et al. reported a 37-year-old Japanese man who had primary LCDD without multiple myeloma. After treatment with a steroid and melphalan, the monoclonal protein became undetectable in his serum and urine and his re-



**Figure 6.** (A) Surgical specimen of the resected kidney revealed severe tubular atrophy and interstitial fibrosis which involved around 90% of the renal cortex. The majority of the glomeruli demonstrated global sclerosis. (B) Interlobular artery disclosed severe arteriosclerosis with medial thickening. (C) Small arterioles showed severe intimal thickening with subendothelial hyalinosis.

nal function remained stable (8). Petrakis et al. reported a 49-year-old caucasian female with LCDD, who was treated with high-dose melphalan and autologous stem cell transplantation, resulting in a significant improvement in the histology and renal function (9).

Although such histological remissions have been demonstrated in LM or immunofluorescences, an improvement of the electron microscopy findings was not described in any of these reported patients. In our case, sequential renal biopsy revealed not only the reduction of the dense deposits and a disappearance of the nodular lesions, but also a reduction of mesangial matrix accumulation by electron microscopy.

The histologic features of LCDD begin with minimal change disease, and then progress to mesangioproliferative and membranoproliferative glomerulonephritis, and finally to characteristic multi-nodular glomerulopathy (10). The detection of monoclonal light chains by immunofluorescence is characteristic of LCDD, and these light chain deposits are always negative for Congo red. The nodules also show abundant lamellar argyrophilia by silver methenamine staining, which indicates that these mesangial nodules are not composed of light chain deposits alone, but also contain excess extracellular matrix (ECM) that has been secreted by mesangial cells exposed to high serum levels of free light chains (11). This is a characteristic difference between LCDD and mesangial-nodular type amyloidosis, which features loss or interruption of argyrophilia due to amyloid deposits. Keeling et al. investigated the molecular mechanism involved in the pathogenesis of LCDD by performing an *in vitro* study (12). They clarified that when mesangial cells were incubated with serum containing excess light chains from patients with LCDD, there was a significant increase in the expression of tenascin-C at the center of the newly formed nodules along with an increased expression of Platelet Derived Growth Factor and Transforming Growth Factor- $\beta$ . They also reported that light chain deposition can induce the production of ECM proteins, such as type IV collagen, laminin, fibronectin, and especially tenascin-C. Thus, the

deposition of light chains in the mesangial region and the subendothelial region of the GBM leads to a secondary increase of the ECM. In our case, long-term clinical remission presumably resulted in the resolution of both mesangial and subendothelial nodular ECM in electron microscopy by the suppression of serum free light chain which stimulates mesangial ECM production.

Fig. 2 suggests that all changes in renal pathology are unaccompanied by significant changes in the patient's proteinuria or serum creatinine. Proteinuria subsided after MP therapy, but the serum creatinine level remained unchangeable. This can be explained by the following hypotheses that MP therapy could cure approximately 20% of affected glomeruli, but could not cure the remaining glomeruli, and these rescued glomeruli might compensate eGFR of approximately 30 mL/min that this patient had before this therapy was initiated.

Recently, the concept of monoclonal gammopathy of renal significance (MGRS) showing all renal disorders caused by monoclonal immunoglobulin secreted from nonmalignant B-cell clone was proposed. MGRS indicates a variety of renal complications associated with systemic lesions induced by the monoclonal immunoglobulin (13).

In conclusion, although MP therapy is one of the classical chemotherapy regimens for multiple myeloma, it is also effective for LCDD with minimal complications by using carefully-controlled dosages. The serial evaluation of renal histology revealed the disappearance of multiple nodular lesions after proteinuria resolved, though light chains on IF persisted and did not disappear. This case may support the hypothesis that nodular lesions in LCDD are caused by the massive production of the ECM stimulated by light chain deposition, and can be reversed to the initial stage, over time, if treatment is successfully continued over the long term.

**The authors state that they have no Conflict of Interest (COI).**

### Financial Support

This study was funded by the Okinaka Memorial Institute for Medical Research.

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