Kidney Medicine

Proximal Tubulopathy With Fibrillary Inclusions: A Rare Manifestation of Lymphoma-Associated Monoclonal Gammopathy of Renal Significance (MGRS)

Ayami Ino, Kanoko Yamaguchi, Sekiko Taneda, Shiho Makabe, Yoshie Wakayama, Hiroshi Kataoka, Junji Tanaka, Kosaku Nitta, and Toshio Mochizuki

Light chain proximal tubulopathy is a rare M-proteinemia–related nephropathy. The inclusions, composed of light chains in light chain proximal tubulopathy, are generally crystalline, and most exhibit a rhombic shape. Noncrystalline structures, such as rods or needle shapes, may also be present. In our patient, one of the noncrystalline structures, fibrillary inclusions in the cytoplasm, were observed, as previously reported in only 4 patients whose primary disease was either multiple myeloma or monoclonal gammopathy of renal significance. This is the first report involving lymphoma. Early diagnosis of light chain proximal tubulopathy is important because those who undergo chemotherapy have an improved kidney prognosis. However, in cases of kidney involvement with blood disorders, thrombocytopenia is often present. Therefore, in our case, open kidney biopsy was selected. Noncrystalline light chain proximal tubulopathy is believed to be less likely to cause Fanconi syndrome. However, Fanconi syndrome was observed in 3 of the 4 patients with fibrillary inclusions. In our case, hypouricemia was improved by chemotherapy, suggesting that the patient presented with Fanconi syndrome. Noncrystalline light chain proximal tubulopathy with fibrillary inclusions may cause Fanconi syndrome, similar to crystalline light chain proximal tubulopathy. We report a case of light chain proximal tubulopathy with fibrillary inclusions complicated by low-grade B-cell lymphoma in which early treatment was successful.

Complete author and article information provided before references.

Correspondence to T. Mochizuki (mtoshi@twmu.ac.jp)

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INTRODUCTION

M-Proteinemia with kidney involvement, monoclonal gammopathy of renal significance, presents with fibrils, microtubular structures, and fine granular crystalline deposits in glomeruli, interstitial kidney tubules, and blood vessels. It presents with a variety of kidney lesions, such as amyloidosis, fibrillary glomerulonephritis, immunotactoid glomerulopathy, cryoglobulinemia, light chain proximal tubulopathy, crystal-storing histiocytosis, monoclonal immunoglobulin deposition disease, and C3 glomerulopathy.[1] In a study of pathology images from 1,078 patients with M-proteinemia–related nephropathy, amyloidosis was most commonly noted (41%), followed by cast nephropathy (27%) and monoclonal immunoglobulin deposition disease (19%). Light chain proximal tubulopathy was rarer (5%).[2]

Light chain proximal tubulopathy occurs when inclusions composed of light chains accumulate in the proximal tubular cytoplasm. The light chains cause an indigestion in the lysosome, resulting in lysosome abnormalities or proximal tubular dysfunction. In terms of clinical presentation, it often presents with reduced kidney function and Fanconi syndrome and has a slow progression, with a rate of developing end-stage kidney disease ranging from 8% to 40%. Chemotherapy is regarded as the preferable choice of treatment.

This case report shares the experience of a patient with light chain proximal tubulopathy involving fibril structures different from the rhomboid crystal structures normally seen as deposits in the proximal tubular cytoplasm.

CASE REPORT

The patient was a woman in her 50s who visited a nearby clinic with the chief symptom of a feeling of abdominal fullness. Along with thrombocytopenia, splenomegaly was indicated, and she was admitted to our hospital 1 month later. Bone marrow biopsy was performed 2 months later, at which point a lymphoproliferative disease such as chronic lymphocytic leukemia was suspected. However, in the absence of a definitive diagnosis, she was kept on follow-up observation. Urinary protein excretion was 0.37 g/g of creatinine (Cr), serum creatinine level was 1.03 mg/dL, and urine β_2-microglobulin (B2M) excretion was 11,831 μg/L (25.7 mg/g Cr). Kidney tubulointerstitial disorder was suspected, but we were unable to perform an ultrasound-guided kidney biopsy due to the thrombocytopenia and continued with the follow-up observation. Kidney function gradually worsened, and $3^1/_2$ years after initial presentation, serum creatinine level was 1.29 mg/dL, urinary protein excretion was 0.84 g/g Cr, and urine B2M excretion was 48,279 μg/L. When she was admitted to our department 2 months later, we obtained the patient's consent to perform an open kidney biopsy.

Except for a 2–finger-width palpation of the spleen under the left rib, physical findings did not reveal anything notable. Urinary protein excretion was 0.8 g/d, urine N-acetyl-β-D-glucosaminidase excretion was 16.6 U/L

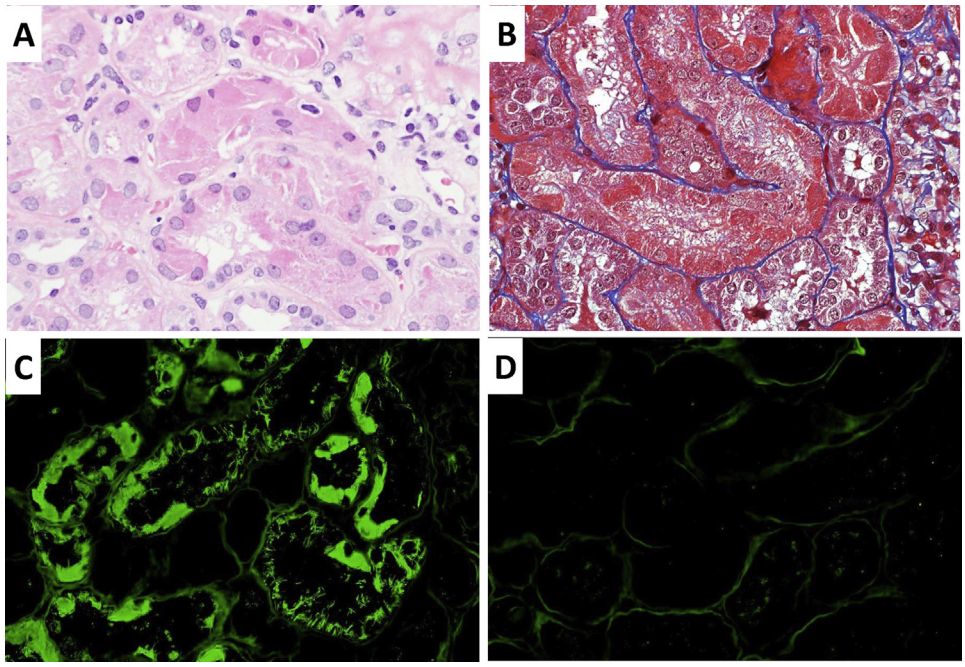

Figure 1. (A, B) Light microscopic and (C, D) immunofluorescence findings. Light microscopy shows slightly swollen proximal tubular cells with (A) eosinophilic cytoplasmic inclusions (hematoxylin and eosin stain) and (B) brightly fuchsinophilic cytoplasmic inclusions (Masson trichrome stain). (C) Positive immunostainings for κ light chain were observed in the proximal tubular epithelium in paraffin-embedded sections by immunofluorescence. (D) No λ light chain deposition was detected (A-D: original magnification, ×400).

(11 U/g Cr), and urine B2M excretion was 174,875 μg/mL (156 mg/g Cr), but she had negative results for Bence-Jones protein. In blood tests, leukocytes were in the normal range, at 4,370/μL, but lymphocytes accounted for 60%. Blood biochemistry testing showed the following values: serum total protein, 8.5 g/dL; serum creatinine, 1.32 mg/dL; estimated glomerular filtration rate, 33.3 mL/min; and C-reactive protein, 0.6 mg/dL. Though there were no obvious findings suggesting Fanconi syndrome, such as renal glycosuria, she exhibited hypouricemia (uric acid, 2.1 mg/dL), with increased fractional excretion of uric acid (37.4%) and clearance of uric acid (14.9 mL/min). An immunoassay revealed that immunoglobulin G (IgG) level was 2,126 mg/dL; IgM, 671 mg/dL; IgG4, 136 mg/dL; free light chains being κ chains, 243 mg/L; and κ:λ ratio, 7.81. Serum immunoelectrophoresis showed IgMκ-type M-protein. Bone marrow examination ruled out multiple myeloma, with plasma cells at 1.0%, but there was an increase in small-type lymphocytic cells with a high nucleo-cytoplasmic ratio at 44.6%. Cells were CD20-positive and weakly CD5- and CD23-positive, suggesting B-cell lymphoproliferative disease. Chronic lymphocytic leukemia and macroglobulinemia were raised as differential diagnoses, but low-grade B-cell lymphoma was ultimately diagnosed.

In the open kidney biopsy, 120 glomeruli were collected, of which 12 were completely sclerotic and 3 had adhesions, but there were no crescents or focal segmental glomerular sclerosis lesions. Some showed a mild increase in mesangial cells or an increase in substrate, but there was no double contour or spike formation of the loop wall. There was mild interstitial fibrosis and tubular atrophy, at 10%. Light microscopy showed slightly swollen proximal tubular cells with cytoplasmic inclusions (Fig 1A and B). Chronic interstitial inflammation was focally observed. Distal tubules and glomeruli were intact. Positive immunostainings for κ light chain were observed in the proximal tubular epithelium in paraffin-embedded section by immunofluorescent (Fig 1C). No λ light chain deposition was detected (Fig 1D). Congo red staining was negative in glomeruli, interstitium, and blood vessels. In light of these findings, the pathologic diagnosis was chronic focal interstitial inflammation with κ light chain deposition in the proximal tubular epithelium. Electron microscopy showed relatively small electron-dense deposits scattered in the mesangial region of the glomeruli, as well as under the endothelium and epithelium.

Meanwhile, numerous fibrils accumulated within the cytoplasm of proximal tubular epithelial cells (Fig 2A). The fibrillary materials tended to be banded and aligned, typically 7 nm in diameter. The fibrils were lying within a single membrane-bound organelle, possibly suggesting a phagolysosome (Fig 2B). Immunoelectron microscopy showed κ light chains on the fibrils of proximal tubular cells, but no λ light chain was detected (Fig 2C and D). Light chain proximal tubulopathy was therefore diagnosed.

Figure 3 shows the clinical course of treatment. Urine B2M level gradually increased, serum creatinine levels

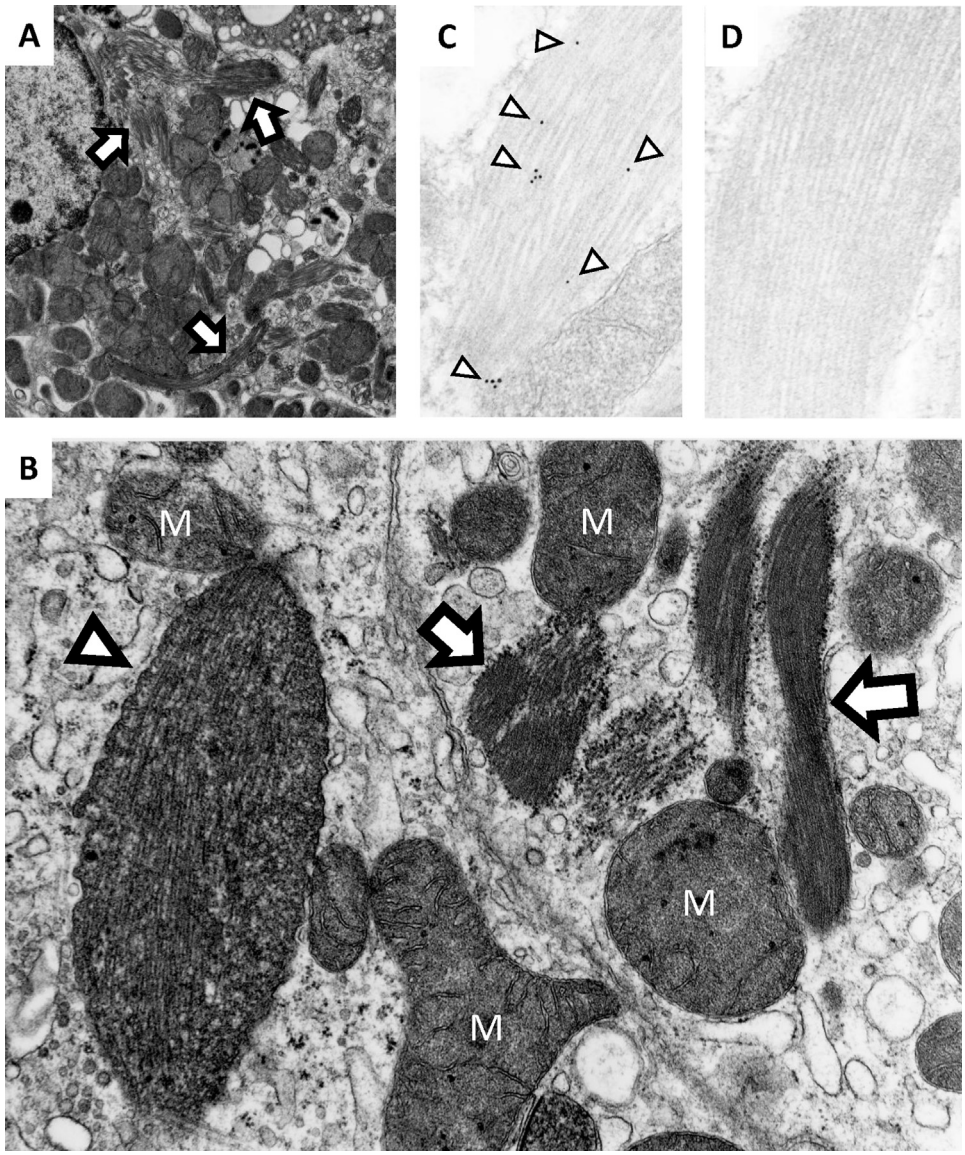

Figure 2. Electron micrographs focusing on the cytoplasm of (A, B) proximal tubular cells and (C, D) immunoelectron microscopic findings. (A) Electron microscopy shows numerous fibrils (arrows) within the cytoplasm of proximal tubular epithelial cells (original magnification, ×4,000). (B) High-power ultrastructural examination reveals that the fibrillary materials (arrows) tended to be banded and aligned, typically 7 nm in diameter. The fibrils were lying within a single membrane-bound organelle, possibly suggesting a phagolysosome (arrowhead) (original magnification, ×15,000). (C, D) Immunoelectron microscopy shows (C) κ light chains on the fibrils of proximal tubular cells (arrowheads), but (D) no λ light chain was detected. Abbreviation: M, mitochondria.

were elevated, and kidney lesions caused by M-proteinemia were believed to be progressing, so the patient was started on bendamustine/rituximab combination therapy 4 months after the open kidney biopsy. Leukopenia and thrombocytopenia bone marrow suppression persisted; therefore, she was switched to rituximab monotherapy 2 months later. Urine B2M and urine N-acetyl-β-D-glucosaminidase excretion decreased, and kidney function also improved (Fig 3). Before treatment, she not only had hypouricemia, but also normal anion gap metabolic acidosis (bicarbonate, 17.3 mmol/L), but the hypouricemia improved (Fig 3).

DISCUSSION

The present case involved light chain proximal tubulopathy with rare fibrillary inclusions, but treatment of the primary disease, low-grade B-cell lymphoma, improved kidney function.

The inclusions, composed of light chains in the proximal tubular cytoplasm with light chain proximal tubulopathy, are generally crystalline and most exhibit a rhombic shape, but other shapes have been reported.[2] A few reports have addressed light chain proximal tubulopathy with non-crystalline structures, but these have often been shown to be diffuse and patchy.[3] These structural differences are

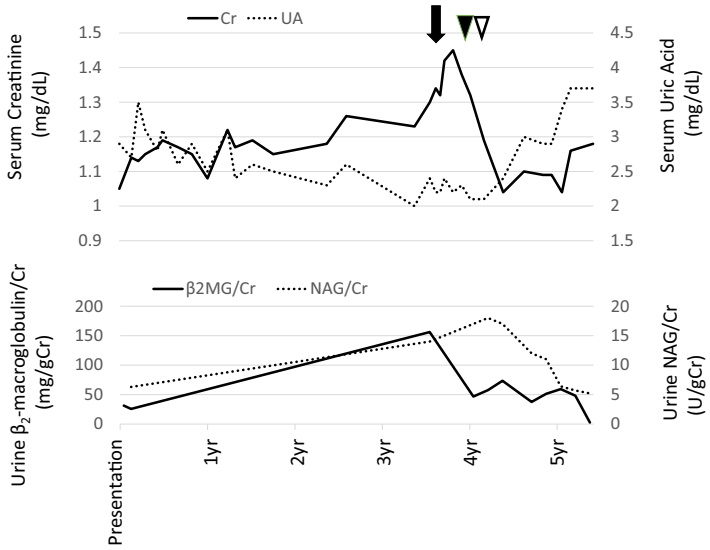

Figure 3. Clinical course. (Upper panel) Solid line indicates serum creatinine (Cr) level and dotted line indicates serum uric acid (UA) level. (Lower panel) Solid line indicates level of urine β_2-microglobulin (β2MG) per urine Cr and dotted line indicates level of urine *N*-acetyl-β-D-glucosaminidase (NAG) per urine Cr. Arrow indicates the date of open kidney biopsy. Black and white arrowheads indicate the starting date of bendamustine/rituximab combination therapy and of rituximab monotherapy, respectively.

considered to be due to differences in protease reactivity or proteolytic enzymes found in the lysosome.[4]

Only 4 patients presenting with fibrillary inclusions in the cytoplasm, as in the present patient, have been previously reported (Table 1).[5-8] The primary disease has been either multiple myeloma or monoclonal gammopathy of undetermined significance, and this is the first report involving lymphoma. Compared with crystalline light chain proximal tubulopathy, noncrystalline light chain proximal tubulopathy is believed to be less likely to cause Fanconi syndrome.[2] However, Fanconi syndrome was observed in 3 of the 4 patients presenting with fibrillary structures, which are classified as noncrystalline light chain proximal tubulopathy. The remaining patient did not present with Fanconi syndrome probably because of the normal kidney function (Table 1).

Though Fanconi syndrome is diagnosed by glucosuria despite a normal blood glucose level, phosphaturia, and aminoaciduria, the present patient had no obvious findings of these criteria. However, she exhibited hypouricemia and metabolic acidosis with an increase in fractional excretion of uric acid and clearance of uric acid, and treatment was followed by a clear improvement in hypouricemia (Fig 3), suggesting that she presented with Fanconi syndrome. In addition, whereas the light chain in frozen sections by immunofluorescence is generally stained in noncrystalline light chain proximal tubulopathy, in our patient, κ light chain failed to be stained in frozen sections but could be stained in paraffin-embedded sections, and the same with crystalline light chain proximal tubulopathy. Considering these facts, noncrystalline light chain proximal tubulopathy presenting with fibrillary structures may differ from noncrystalline light chain proximal tubulopathy not involving fibrillary structures in being more likely to cause Fanconi syndrome, similar to crystalline light chain proximal tubulopathy.

Early diagnosis of light chain proximal tubulopathy is important because those who have undergone chemotherapy have an improvement in kidney prognosis, and having a high estimated glomerular filtration rate before treatment is a positive factor for kidney prognosis.[2] However, in cases of kidney involvement with blood disorders, thrombocytopenia is often present, and kidney biopsy is generally not performed. However, it is also often the case that the treatment strategy is decided based on kidney pathologic findings, as in the present case, and thus open kidney biopsy should also be actively considered. The kidney function decline prompted us to perform an open kidney biopsy, which was the basis for the

Table 1. Case Reports of light Chain Proximal Tubulopathy With Fibrillary Structure

Case	Primary Disease	M-Protein	Serum Creatinine, mg/dL	Fanconi Syndrome	Coexistant Nephropathy	Light Chain in Cytoplasm	Diameter of Fibers, nm	Reference
1	MM	BJP-κ	2.8	+	–	κ	15-20	5
2	MM	IgG-κ	0.9	–	–	κ	6	6
3	MM	BJP-λ	1.8	+	Cast nephropathy	λ	ND	7
4	MGUS	BJP-κ	3	+	–	κ	ND	8
Present case	B-cell lymphoma	IgM-κ	1.2	+ (?)	-	κ	7	-

Abbreviations: BJP, Bence-Jones protein; IgG, immunoglobulin G; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; ND, not detected.

treatment that ensured an improvement in kidney function.

In conclusion, for patients with monoclonal gammopathy of undetermined significance, we should actively consider kidney biopsy for the diagnosis of kidney involvement and decision making for treatment of the primary disease.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Ayami Ino, MD, PhD, Kanoko Yamaguchi, Sekiko Taneda, MD, PhD, Shiho Makabe, MD, Yoshie Wakayama, MD, PhD, Hiroshi Kataoka, MD, PhD, Junji Tanaka, MD, PhD, Kosaku Nitta, MD, PhD, and Toshio Mochizuki, MD, PhD.

Authors' Affiliations: Department of Medicine, Kidney Center (AI, SM, YW, HK, KN, TM), Tokyo Women's Medical University (KY); Department of Pathology (ST), Clinical Research Division for Polycystic Kidney Disease, Department of Medicine, Kidney Center (HK, TM), and Department of Hematology (JT), Tokyo Women's Medical University, Tokyo, Japan.

Address for Correspondence: Toshio Mochizuki, MD, PhD, Department of Medicine, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: mtoshi@twmu.ac.jp

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