Remission of light chain proximal tubulopathy in IgG λ -type multiple myeloma by lenalidomide and dexamethasone therapy

Shinya Kawamoto¹ · Yuji Hidaka¹ · Yu Kaneko¹ · Hideo Misawa¹ · Katsuhiko Nagahori¹ · Atsunori Yoshino¹ · Takamitsu Okamura² · Shinichi Ban³ · Yoshihiko Ueda³ · Tetsuro Takeda¹

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Abstract

Light chain proximal tubulopathy is a rare manifestation of monoclonal gammopathy. A 73-year-old Japanese woman was noted to have urinary protein and hypertension on health examination and visited the regional clinic. She was noted to have IgG λ M protein and suspected of multiple myeloma. She was referred to us with massive proteinuria (7.5 g/g creatinine) and Bence Jones proteinuria without renal dysfunction. A renal biopsy revealed no glomerular abnormalities, but a tubular cast was observed partially in tubules without tubular atrophy or a crystalline structure. Direct Fast Scarlet staining was absent both in glomerulus and vascular wall. Immunofluorescence revealed λ light chain (LC) staining in the proximal tubules. Electron microscopy revealed nonspecific findings including increased lysosomes with irregular contours and mottled appearance. A bone marrow biopsy revealed plasma cell proliferation (35%) and multiple myeloma immunoglobulin G λ type. She showed progressive anemia and decrease of eGFR with elevated level of urinary β -2 microglobulin. She was treated with lenalidomide + dexamethasone (Ld). With Ld therapy, she achieved hematologic and nephrologic remission reducing the free LC, λ/κ ratio, urinary protein level, and urinary β -2 microglobulin level.

Keywords Light chain proximal tubulopathy · Multiple myeloma · IgG lambda M protein · Lenalidomide

Introduction

Plasma cell dyscrasias such as multiple myeloma (MM) result from the clonal proliferation of plasma cells and subsequent overproduction of immunoglobulins, including free light chains. Renal dysfunction is a core manifestation of plasma cell dyscrasias. A broad range of kidney pathogenesis can occur, including light chain cast nephropathy, monoclonal immunoglobulin (Ig) deposition disease, light chain

amyloidosis, light chain proximal tubulopathy (LCPT), and tubulointerstitial nephritis [1–3].

Free light chains (FLCs) are low molecular weight proteins that are normally produced in abundance by the lymphoid tissue (around 500 mg/day). They are relatively freely filtered at the glomerulus and reabsorbed and hydrolyzed very efficiently by the proximal tubules via clathrin-dependent endocytosis by the megalin/cubilin receptor system, such that only 1–10 mg of FLCs appear in the urine daily [4]. The overproduction of monoclonal FLCs, particularly in the setting of MM, often overcomes the capacity of the proximal tubular epithelium to process all filtered FLCs, leading to overflow proteinuria. A large amount of free LC is produced that cannot be completely reabsorbed in the proximal renal tubule, causing proximal tubular damage. LCPT, a rare manifestation of monoclonal gammopathy, is characterized by cytoplasmic inclusions of monoclonal LC within proximal tubular epithelial cells [5].

✉ Shinya Kawamoto
kwmt@dokkyomed.ac.jp

¹ Department of Nephrology, Dokkyo Medical University Saitama Medical Center, 2-1-50 Minamikoshigaya, Koshigaya, Saitama 343-8555, Japan

² Department of Internal Medicine, Dokkyo Medical University Saitama Medical Center, 2-1-50 Minamikoshigaya, Koshigaya, Saitama 343-8555, Japan

³ Department of Pathology, Dokkyo Medical University Saitama Medical Center, 2-1-50 Minamikoshigaya, Koshigaya, Saitama 343-8555, Japan

Case

A 73-year-old Japanese woman who had no history of urinary abnormalities until 1 year prior to admission was noted to have urinary protein and hypertension on a health examination and visited the regional clinic for further investigations. She had immunoglobulin G (IgG) λ M protein and was suspected of having MM. She was referred to our hospital for further evaluation and treatment.

On admission, the patient was 139 cm tall, weighed 41.4 kg, and had a blood pressure of 147/96 mmHg, pulse of 93/min, and temperature of 36.3 °C. Cardiac, pulmonary, and abdominal examination findings were unremarkable.

Laboratory data were as follows (Table 1). Urinalysis revealed massive proteinuria (2+, 3.6 g/day) without hematuria and positive for Bence Jones protein. The urinary β -2microglobulin (β -2MG) level was 678 ng/mL. Laboratory testing revealed normal values of serum total protein (8.2 g/dL), albumin (4.6 g/dL), creatinine (0.5 mg/dL), uric acid (3.3 mg/dL), and HCO_3 (27 nmol/mL). Serum immunoglobulin G was 1910 mg/dL with suppression of immunoglobulin A (IgA 16.4 mg/dL) and immunoglobulin M (IgM 7.0 mg/dL). Level of third complement component (C3) was 82 mg/dL (normal 50–130 mg/dL); the fourth component (C4) level was 19 mg/dL (normal 10–50 mg/dL); hemolytic complement activity

via the classical pathway (CH50) was 16 U/mL (normal 25.0–48.0 U/mL). Serum protein electrophoresis showed an M-spike with monoclonal IgG λ . Urinary protein electrophoresis with immunofixation also showed a monoclonal λ Bence Jones protein. FLC κ was 1.4 mg/L and λ was 2350 mg/L for a λ/κ ratio of 1679.

A bone marrow examination revealed hypocellular marrow with 35% atypical plasma cells. Ninety percent of the plasma cells were positive for CD138 and λ chain despite being negative for κ chain, IgG, IgA, and IgM.

A renal biopsy revealed that all seven glomeruli were present without significant pathologic alternations, but a tubular cast was observed partially in tubules without tubular atrophy or a crystalline structure. The proximal tubular cells are variably distended with reactive nuclei, droplets/globules and vacuoles (Fig. 1). Direct Fast Scarlet staining was absent both in glomerulus and vascular wall. Immune deposits of IgG, IgA, IgM, C1q, C3c, C3d, C4c, fibrinogen, κ light chains, and λ light chains were absent in the glomerulus (Fig. 2). Only λ light chains were positive in the tubules and the urinary cast. We also performed immunohistochemical staining for κ , λ , CD10 (proximal tubules), and epithelial membrane antigen (distal tubules) to identify the tubule level. The materials for immunofluorostains (κ , λ) and immunohistochemistry (CD10, EMA) were using formalin-fixed paraffin-embedded serial sections. IF were performed using re-embedding material from fixed paraffin-embedded section. The immunohistochemical staining revealed that

Table 1 Laboratory findings

Peripheral blood		Blood chemistry		Immunological findings	
WBC	2600/ μL	AST	34 IU/L	CRP	0.5 mg/dL
RBC	$380 \times 10^4/\mu\text{L}$	ALT	22 IU/L	HBsAg	(–)
Hgb	12.4 g/dL	ALP	173 IU/L	HCV Ab	(–)
Hct	34.9%	γGTP	14 IU/L	TPHA	(–)
Plt	$18.7 \times 10^4/\mu\text{L}$	LDH	251 IU/L	IgG	1910 mg/dL
Urine		TP	8.2 g/dL	IgA	16.4 mg/dL
pH	7	Alb	4.6 g/dL	IgM	7 mg/dL
SG	1.02	TC	207 mg/dL	C3	82 mg/dL
Protein	(2+)	TG	85 mg/dL	C4	19 mg/dL
	7.8 g/gCr	Na	137 mEq/L	CH50	16 IU/mL
	3.6 g/day	K	4.1 mEq/L	MPO–ANCA	< 10 U/mL
Occult blood	(–)	Cl	101 mEq/L	PR3–ANCA	< 10 U/mL
Glucose	(–)	Ca	9.9 mg/dL	Anti GBM Ab	< 10
Ketone	(–)	P	3.7 mg/dL	ANA	320
β 2MG	678 ng/mL	%TRP	74.4%		Speckled
BJP	(+)	HCO_3	27 nmol/L	Free light chain	
Urine sediment		BUN	15 mg/dL	κ	1.4 mg/L
RBC	4/HPF	Cre	0.5 mg/dL	λ	2350 mg/L
WBC	1/HPF	UA	3.3 mg/dL	λ/κ ratio	1679
		Glu	122 mg/dL		
		HbA1c	5.2%

Fig. 1 Renal biopsy findings light microscopy. **a** Masson Trichrome stain; $\times 40$. **b** Periodic acid–Schiff (PAS) stain; $\times 400$. **c** Masson Trichrome stain; magnification $\times 400$. **d** Periodic acid–Schiff (PAS) stain; $\times 400$. Light microscopy images show no remarkable glomeru-

lar changes. Tubular casts were observed partially in tubules without tubular atrophy or a crystalline structure. The proximal tubular cells are variably distended with reactive nuclei, droplets/globules and vacuoles

the λ light chain-positive tubules were at the proximal level (Fig. 3). Electron microscopy revealed nonspecific findings include increased lysosomes with irregular contours and mottled appearance (arrows) without either crystal formation or bundles (Fig. 4). This change is also nonspecific, but commonly present in this LCPT subtype (without organized inclusion).

Her renal manifestation was diagnosed as LCPT due to MM findings on renal biopsy.

Clinical follow-up (Fig. 5)

At the time of LCPT diagnosis, considering her advanced age (73 years) and lack of nephrology and hematology symptoms, the patient chose follow-up observations rather than chemotherapy. However, the FLC λ increased to 6620 mg/dL (λ/κ ratio of 2758) with elevation of urinary β -2MG to 14,150 ng/mL 8 months after the renal biopsy. Her estimated glomerular filtration rate (eGFR) decreased from 87 to 47 mL/min/1.73 m² and she developed progressive anemia (Hb 10 g/

dL). Ld therapy (lenalidomide 15 mg/day, on days 1 through 21 in combination with dexamethasone 40 mg/day once a week (day 1, 8, 15, 22) of each 28-day cycle) was initiated. The Ld therapy reduced the light chain, λ/κ ratio, urinary protein level, and urinary β -2MG level and increased the eGFR. After 6 cycles of the Ld therapy, she achieved hematologic remission, the proteinuria resolved, urinary β -2MG decreased to 1100 ng/dL, and eGFR increased to 56 mL/min/1.73 m² without major complication. Ixazomib [4 mg/day once a week for 2 weeks (day 1, 8, 15)] was added on Ld therapy as iLd treatment for maintenance therapy. 1 year after treatment, she is fine and maintained remission as FLC κ was 2.0 mg/L and λ was 65.2 mg/dL for a λ/κ ratio of 32.6, urinary β -2MG decreased to 660 ng/dL, eGFR 55 mL/min/1.73 m².

Discussion

LCPT associated with plasma cell dyscrasias is a rare abnormality. The prevalence of LCPT is reportedly low (2.5–5%) among dysproteinemia-related renal disease [6–8]. However,

Fig. 2 Immunofluorescent findings of immunoglobulin and complement. Immune deposits of IgG, IgA, IgM, C1q, C3c, C3d, C4c, fibrinogen, κ and λ light chains were absent in glomerulus

the true incidence of LCPT is unknown because a renal biopsy has a bias in patients with unexplained renal insufficiency and/or significant proteinuria. The IF staining features of FLC and electron microscopic appearance of inclusion were specific and varied. Cases of κ -light chain storage are more common than those of λ , and crystal formation may be associated with light chain subtype. Stokes reported that 40 of 46 light chains were κ [8]. Crystalline LCPT is almost exclusively seen in κ -restricted disease with rare examples of λ -restricted intracytoplasmic crystals [6, 9]. Although the reason for the κ predominance is not yet clearly understood, resistance to enzymes in the lysosome is considered one reason. Stokes reported that most patients had proteinuria (98%) and renal insufficiency (83%). Urinary protein excretion was often heavy (> 1 g/day in 87% and > 3 g/day in 37%), but hypoalbuminemia was not seen [8]. This means the proteinuria consisted predominantly of FLC rather than albumin. These characteristics were consistent in this case.

One-third of LCPT patients, all with crystalline LCPT, had one or more features of Fanconi syndrome (FS), including normoglycemic glycosuria, metabolic acidosis, hypophosphatemia, bone pain, and aminoaciduria. FS often triggers the suspicion of LCPT [10, 11]. This case was λ -type FLC without crystalline LCPT and did not show any signs of FS as in Stokes' review [8].

FS is uncommon in adults and more often signifies the presence of a plasma cell dyscrasia. The propensity for the light chains in LCFS (light chain Fanconi syndrome) to form crystals that precipitate in cytoplasm of proximal tubules appears to be determined by their amino acid sequences and the resultant physical and chemical properties. Aucounturier reported characterization of a monoclonal κ -cDNA from a LCFS patient closely fit into the VK1 subgroup [12]. Protease treatment of the light chain produced an elongated NH_2 -terminal fragment of the variable (V) domain that was resistant to further degradation and was able to form crystals when bound to itself or intact κ -light chains.

Most crystalline LCPT cases require pronase digestion of formalin-fixed sections for the detection of monoclonal light chains, whereas non-crystalline LCPT can be detected by immunofluorescence microscopy (IF) of frozen tissue in all patients [13]. This also matches our diagnosis using only IF and not by using pronase digestion of formalin-fixed sections in this case of non-crystalline LCPT.

Stokes reported follow-up outcomes of 30 crystalline LCPT and 6 non-crystalline LCPT cases as median kidney survival of 135 months and 64 months, respectively. Stokes reported that the morphologic findings of light chain crystalline inclusions in the proximal tubular cytoplasm are often not a harbinger of progressive renal

Fig. 3 Immunofluorescent findings of κ and λ light chains and immunohistochemical staining of CD10 and epithelial membrane antigen (EMA) in tubulus, original magnification $\times 100$. κ light chain was

absent, but λ light chain was positive in tubules. Distribution of λ light chain-positive tubulus was same as CD10 positive tubulus

Fig. 4 Electron microscopic findings. **a** Low power field, **b** high power field. Electron microscopy findings include lysosomes with irregular contours and mottled appearance (arrow) without either crystal formation or bundles in proximal tubules

Fig. 5 Clinical course

failure. Non-crystalline LCPT was particularly uncommon in the study by Stokes and colleagues (only 6 cases). The significance of light chain proximal tubulopathy without crystal formation is debatable. Specifically, whether the findings shown here represent a true lesion or simply a physiologic process in the setting of excess free light chains. This is an important distinction considering the fact that end organ damage is frequently used in treatment algorithms for plasma cell dyscrasia. If this is merely a physiologic process in the setting of excess FLC then this is best considered a coincidental finding and not an indication for treatment of the plasma cell dyscrasia. Alternatively, if this is determined to be a lesion resulting from the presence of excessive and aberrant free light chains, treatment of the underlying plasma cell dyscrasia is warranted in many cases based on this finding. This case supported that non-crystalline LCPT cases preserved kidney function despite persistent massive light chain proteinuria, but it was exacerbated within few months both hematologically and nephrologically when follow-up without treatment, and remission was achieved by chemotherapy. So more patients need to be studied in future to determine if there are significant clinical and prognostic differences between crystalline and non-crystalline LCPT.

The International Kidney and Monoclonal Gammopathy Research Group recommends chemotherapy or stem cell transplantation for LCPT even before worsening hematologic disease occurs [14]. Kidney function showed a general improvement trend in patients who were treated with chemotherapy alone or chemotherapy and stem cell transplantation [8]. Furthermore, renal involvement is an independent predictor of poor outcomes in MM [15], and early identification of LCPT may help stratify risk factors and drive patient management.

This case did not show major renal manifestations such as acute kidney injury by cast nephropathy, AL amyloidosis, monoclonal immunoglobulin deposition disease, or FS. In this case, careful observation of tubules enabled the diagnosis of LCPT despite absence of any signs of acute tubular injury or tubular dysfunction as in cases of FS.

Initially, this case was follow-up without chemotherapy considering her elderly and asymptomatic, but treatment after 8 months was successful. Lenalidomide, an immunomodulatory drug, has been shown to improve the outcomes of patients with newly diagnosed, previously treated or refractory MM [16, 17]. Lenalidomide has been shown to induce apoptosis of MM cells and inhibit angiogenesis and blocks the binding of MM cells to the bone marrow stromal cells [18]. Recently Kimura reported three cases of light chain deposition disease (LCDD) treated with lenalidomide therapy, resulting in hematologic responses accompanied by a significant reduction in proteinuria and improvement in the renal function [19]. With recent advances in the treatment of myeloma by proteasome inhibitor and lenalidomide, early intervention should be considered if monoclonal gammopathy of undetermined significance (MGUS) also presents as MGRS.

Further pathological and clinical investigations of future cases are required and important to further our understanding of this disease entity.

Conclusion

Here, we reported a case of LCPT without Fanconi syndrome in IgG λ-type multiple myeloma as a rare manifestation of paraproteinemia that was successfully treated with Ld therapy.

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Compliance with ethical standards

Conflict of interest All authors declare no competing interests.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from participants included in the article.

References

- Leung N, Nasr SH. Myeloma-related kidney disease. *Adv Chronic Kidney Dis.* 2014;21:36–47.
- Kyle RA, Gertz MA, Witzig TE. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc.* 2003;78:21–33.
- Nasr SH, Valeri AM, Sethi S. Clinicopathologic correlations in multiple myeloma: a case series of 190 patients with kidney biopsies. 2012;5+:786–794.
- Herlitz LC, D'Agati VD, Markowitz GS. Crystalline nephropathies. *Arch Pathol Lab Med.* 2012;136:713–20.
- Herrera GA. Proximal tubulopathies monoclonal light chain mediated (proximal light chain tubulopathy). In: Jennette JC, editor. *Heptinstall's pathology of the kidney*, 7th ed. Philadelphia: Wolters Kluwer; 2015. pp. 959–63.
- Larsen CP, Bell JM, Harris AA. The morphologic spectrum and clinical significance of light chain proximal tubulopathy with and without crystal formation. *Mod Pathol.* 2011;24:1462–9.
- Herrera GA. Proximal tubulopathies associated with monoclonal light chains: the spectrum of clinicopathologic manifestations and molecular pathogenesis. *Arch Pathol Lab Med.* 2014;138:1365–80.
- Stokes MB, Valeri AM, Herlitz L, Khan AM, Sjogel DS, Markowitz GS, D'Agati VD. Light chain proximal tubulopathy: clinical and pathologic characteristics in the modern treatment era. *J Am Soc Nephrol.* 2016;27:1555–65.
- Gallan AJ, Khalighi MA. Lambda light chain crystalline cast nephropathy and proximal tubulopathy. *Kidney Int Rep.* 2016;1(4):316–20.
- Yamashige M, Gotoh S, Nakano J, Gotoh K, Nakai K, Fujii H, Hara S, Nishi S. A case of Fanconi syndrome due to light chain proximal tubulopathy. *J Jpn Soc Intern Med.* 2017;106(4):813–7.
- Herlitz LC, Roglieri J, Resta R, Bhagat G, Markowitz GS. Light chain proximal tubulopathy. *Kidney Int.* 2009;76:792–7.
- Aucounturier P, Bauwens M, Khamlichi AA, Denoroy L, Spinelli S, Touchard G, Preud'homme JL, Cogné M. Monoclonal Ig L chain and L chain V domain fragment crystallization in myeloma-associated Fanconi syndrome. *J Immunol.* 1993;150:3561–8.
- Nasr SH, Galgano SJ, Markowitz GS, Stokes MB, D'Agati VD. Immunofluorescence on pronase-digested paraffin sections: a valuable salvage technique for renal biopsies. *Kidney Int.* 2006;70:2148–51.
- Fernand JP, Bridoux F, Kyle RA. How I treat monoclonal gammopathy of renal significance (MGRS). *Blood.* 2013;122:3583–90.
- Korbet SM, Schwartz MM. Multiple myeloma. *J Am Soc Nephrol.* 2006;17:2533–45.
- Dimopoulos M, Spencer A, Attal M, Prince M, Harousseau JL, Dmoszynska A, Miguel JS, Hellmann A, Facon T, Foà R, Corso A, Masliak Z. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med.* 2007;357:2123–32.
- McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, Giralt S, Stadtmauer EA, Weisdorf DJ, Vij R, Moreb JS, Callander NS. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2012;366:1770–81.
- Furukawa M, Ohkawara H, Ogawa K, Ikeda K, Ueda K, Nakamura AS, Ito M, Imai J, Yanagisawa Y, Honma R, Watanabe S, Waguri S, Ikezoe T, Takahashi H. Autocrine and paracrine interactions between multiple myeloma cells and bone marrow stromal cells by growth arrest-specific gene 6 cross-talk with interleukin-6. *J Biol Chem.* 2017;292:4280–92.
- Kimura S, Ohkawara H, Ogawa K, Tanaka M, Sano T, Shirado HK, Takahashi H, Ueda K, Nakamura AS, Matsumoto H, Kazama JJ, Hashimoto Y, Ikezoe T. Lenalidomide as a beneficial treatment option for renal impairment caused by light chain deposition disease: a case series. *Intern Med Adv Publ.* <https://doi.org/10.2169/internalmedicine.1018-18>.

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