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【 CASE REPORT 】

Lambda Light Chain Non-crystalline Proximal Tubulopathy with IgD Lambda Myeloma

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Abstract:
Light Chain Proximal Tubulopathy (LCPT) is a rare form of paraprotein-related kidney disease in which monoclonal free light chains damage the proximal renal tubular epithelial cells. We herein report the case of a 78-year-old woman who presented with anemia and kidney dysfunction. Serum and urine protein electrophoresis analyses revealed a monoclonal IgD and λ free light chains. Proximal tubular injury and the accumulation of λ light chains were found by kidney biopsy. Electron microscopy revealed no organized structure suggestive of crystals. LCPT was caused by IgD lambda myeloma and bortezomib and dexamethasone therapy led to very good partial response (VGPR) without a worsening of the kidney function.

Key words: Light Chain Proximal Tubulopathy (LCPT), IgD λ myeloma, paraprotein related kidney disease

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Introduction

An abnormal immunoglobulin produced from B lymphocytes/plasma cells causes renal impairment. Patients with paraprotein-related kidney disease present with various manifestations, including light chain cast nephropathy, monoclonal Ig deposition disease, light chain amyloidosis, light chain proximal tubulopathy (LCPT), and tubulointerstitial nephritis (1). LCPT is a rare condition in which monoclonal free light chains damage the proximal renal tubular epithelial cells. The accumulated light chains frequently form crystals and LCPT is classified into crystalline or non-crystalline LCPT, based on the presence or absence of a crystal structure in the tubular cytoplasm. The latter is even rarer (2). Although the prognosis of LCPT is not well known because of the small number of cases, there are reports of patients who have developed end-stage kidney disease (2). It is considered very important to accumulate cases in order to establish the definition of the disease entity and determine the appropriate therapy. In this report, we present a case of non-crystalline LCPT that was successfully managed with bortezomib and dexamethasone therapy.

Case Report

A 78-year-old woman was referred to our nephrology clinic for the evaluation of an elevated serum creatinine level and anemia. She had been followed by her primary care physician because of reflux esophagitis and dyslipidemia for approximately 20 years. She had been undergoing regular checks; however, no urinalysis abnormalities or kidney dysfunction had ever been pointed out. Her care was interrupted after her husband died. At approximately three months before her referral, she noticed a loss of appetite and general malaise. She then visited her primary physician for the first time in eight months. At that visit, anemia and kidney dysfunction were detected.

At the patient's first visit to our department, a physical examination revealed pale conjunctiva and hypertension

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Table. Laboratory Data before Kidney Biopsy.

Urinalysis		Reference range
specific gravity	1.014	
pH	5.5	
protein	1+	
protein/Creatinine	7.034	g/gCre
glucose	-	
occult Blood	-	
RBC	0-1	/HPF
WBC	0-1	/HPF
Hyaline Cast	0-1	/HPF
Granular Cast	0-1	/HPF

CBC		Reference range
WBC	5.6	4.0-9.0 $\times 10^3/\mu L$
neutro	66.2	%
eosino	1.2	%
lympho	27.1	%
mono	4.4	%
RBC	2.46	3.9-4.9 $\times 10^6/\mu L$
Hb	8.3	11.5-14.5 g/dL
Ht	25	34-43 %
Plt	395	150-350 $\times 10^3/\mu L$
Blood coagulation test		
PT-INR	0.94	0.85-1.15
APTT	30.6	24.3-35.0 sec
Fib	443	174-404 mg/dL

Chemistry		Reference range
BUN	41	8-20 mg/dL
Cre	2.61	0.4-0.9 mg/dL
UA	6.8	2.0-7.0 mg/dL
eGFR	14.32	mL/min/1.73m^2
Na	144	135-146 mEq/L
K	4.4	3.5-4.8 mEq/L
Cl	109	98-108 mEq/L
Ca	8.9	8.8-10.1 mg/dL
P	4.1	2.4-4.6 mg/dL
Mg	2.5	1.6-2.3 mg/dL
T.prot	6.9	6.5-8.2 g/dL
Alb	4	3.9-4.9 g/dL
alpha1	3.9	1.9-2.9 %
alpha2	10.5	5.1-8.9 %
beta	11.8	6.5-10.8 %
gamma	14.5	10.6-20.9 %
T-Cho	235	130-220 mg/dL
TG	243	35-150 mg/dL
HDL-C	45	40-100 mg/dL
GOT	21	10-35 IU/L
GPT	14	5-40 IU/L
LDH	230	110-220 IU/L
ALP	309	100-340 IU/L
γ-GT	45	0-30 IU/L
Glucose	105	<126 mg/dL

Serology		
CRP	0.48	<0.3 mg/dL
RF	<10	<10 IU/mL
ANA	-	-
IgG	695	870-1,700 mg/dL
IgA	94	110-410 mg/dL
IgM	22	46-260 mg/dL
IgD	415	<9 mg/dL
IgE	239.7	<170 IU/dL
C3	118	65-135 mg/dL
C4	59	13-35 mg/dL
CH50	67	32-49 mg/dL
HBs Ag	-	-
HCV Ab	-	-

(161/74 mmHg). Peripheral edema was not observed and there were no signs of fluid overload. No abnormalities were detected in the lungs, heart, abdomen, or extremities. A urinalysis showed proteinuria (7.03 g/gCre) without hematuria (0-1/HPF), without glycosuria. Laboratory data revealed anemia (hemoglobin: 9.8 g/dL), elevated blood urea nitrogen [from 19.8 mg/dL (15 months before referral) to 41 mg/dL] and creatinine [from 0.44 mg/dL (15 months before referral) to 2.61 mg/dl], low IgG [695 mg/dL, reference range (870-1,100 mg/dL)], IgA [94 mg/dL (110-410 mg/dL)] and IgM levels [22 mg/dL, (46-210 mg/dL)]. Her IgD level was elevated [415 mg/dL, (<9 mg/dL)]. Neither hypophosphatemia nor hypouricemia were detected. Serum electrophoresis and immunofixation revealed a monoclonal IgD and monoclonal λ free light chains and urine protein electrophoresis revealed monoclonal λ free light chains. A laboratory analysis showed that the patient's serum free λ light chain level was remarkably elevated, [4,500 mg/L, (3.3-19.4 mg/L)] and that her free κ light chain level was slightly elevated [42.6 mg/L, (5.7- 26.3 mg/L)]. The κ/λ ratio was 0.01 [reference range, 0.26-1.65]. The patient's urinary N-acetyl-β-D-glucosaminidase [115.7 U/I, (<11.2 U/I)] and β2 microglobulin [19,723 μg/L, (<360 μg/L)] levels were elevated and Gallium 67 scintigraphy showed weak uptake in the bilateral kidneys, suggesting an active inflammation process in the kidneys. To determine the cause of kidney dysfunction, kidney biopsy was performed. The laboratory data before the renal biopsy are shown in Table.

Kidney biopsy

Two kidney tissue cores were obtained. Light microscopy revealed no major glomerular abnormalities. In the tubules and interstitium, we observed both enlarged tubules and atrophic tubules. The enlarged proximal tubules showed swelling (arrow), loss of brush border (surrounded by a dotted line), and detachment from the basement membrane (arrowhead). Lymphocytic infiltration was also observed in part of the interstitium (Fig. 1A and B). Casts were noted in the distal tubules. However, the burden of the casts was not so extensive and inflammatory cell infiltration was mild. Severe (>50%) tubular atrophy and interstitial fibrosis (Masson's trichrome-positive) were observed (Fig. 1C), along with arterial and arteriolar thickening (not shown in the figure) suggesting some chronicity of the disease process.

Immunofluorescence microscopy revealed no immune deposits in the glomeruli, while the tubules were found to be filled with droplets in which λ light chains were brightly stained; κ light chains were not detected (Fig. 1D and E). We found that the proximal tubules, which reabsorbed the λ light chains, were injured (KIM-1-positive) (Fig. 1F). DNA damage (γH2AX positive) (3) was found in the injured (KIM-1 positive) proximal tubules (Fig. 1G). No crystalline structures were found and vacuolar degeneration was seen in the proximal tubular cytoplasm under an electron microscope (Fig. 1H and I). No amyloid deposits were seen in the kidney. We concluded that the proximal tubular injury was the main etiology of the kidney dysfunction in this case; however, both LCPT and mild cast nephropathy in the distal tubules might have contributed to the pathophysiology.

Diagnosis

Non-crystalline Light Chain Proximal Tubulopathy

Clinical follow up

The bone marrow biopsy findings were compatible with multiple myeloma with >10% of the plasma cells (34.6%) being positive for monoclonal λ light chains. Imaging studies showed evidence of lytic lesions in the lumbar spine. She was diagnosed with multiple myeloma (IgD-λ type: Durie and Salmon IIB, ISS III) based on the fulfillment of the following criteria: clonal bone marrow plasma cells ≥ 10%, anemia, renal insufficiency and bone lesions (4). She was treated with bortezomib and dexamethasone. After two courses of treatment, her urinary N-acetyl-β-D-glucosaminidase (115.7 U/L to 3.1 U/L) and β2 microglobulin (19,723 μg/L to 8,055 μg/L) levels were decreased, which suggested the improvement of her active tubular injuries. Bortezomib and dexamethasone treatment resulted in a very good partial response (VGPR). Her kidney function remained stable, with her estimated glomerular filtration rate (eGFR) remaining approximately 15 mL/min/1.73 m^2; her urinary protein excretion also decreased to <0.5 g/gCre (Fig. 2).

Discussion

LCPT is a rare form of paraprotein-related kidney disease in which inclusion bodies consisting of free light chains (FLCs) accumulate in the cytoplasm of the proximal tubules (2). FLCs are low molecular-weight proteins that are normally produced by lymphoid tissues. Under normal circumstances, approximately 500 mg are produced per day and the FLCs are reabsorbed and hydrolyzed very efficiently in the proximal tubules by the megalin/cubilin receptor system after glomerular filtration. As a result, only 1-10 mg/day are excreted in the urine (5). In addition to the overproduction of FLCs, the uptake of FLCs by endocytosis affects the pathogenesis of LCPT. Active reabsorption in the proximal tubules is sometimes strongly associated with the onset of disease and the nature of the substance reabsorbed in the proximal tubule is largely related to the development of kidney injury (6).

Monoclonal FLCs are cytotoxic and redox signaling following the endocytosis of FLCs causes increased oxidative stress and inflammatory cytokine production, which leads to apoptosis in the proximal tubular cells (7). On the other hand, there is an optimal environment for coprecipitation of FLCs with Tamm-Horsfall glycoprotein (THP) in the distal tubules. Excessive FLCs form casts, obstruct the tubular lumen and may lead to rupture and secondary inflammation (1, 5, 6, 8) (Fig. 3). Although crystalline deposits are classified based on the presence or absence of a crystal structure, the significance of crystalline versus non-crystalline LCPT remains unknown.

While cast nephropathy tends to cause AKI in myeloma, LCPT shows a wide variety of disease phenotype, ranging from subtle tubule transport disorders to tubule cell death (apoptosis or necrosis). LCPT is mainly caused by κ chain, rarely by λ chain and λ type FLCs often display acute tubular injury. The presence or severity of acute tubular injury did not correlate with kidney function at presentation or the prognosis. As seen in our case, non-crystalline LCPT usually does not develop Fanconi syndrome, though it is common in crystalline LCPT. The incidence of Fanconi syndrome in crystalline LCPT is approximately 43% (1, 2).

The optimal treatment of paraprotein-related kidney diseases, including LCPT, when the bone marrow findings are associated with low-mass multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), and has not been determined (9, 10). In recent years, the concept of monoclonal gammopathy of renal significance (MGRS) with bone marrow plasma cells <10% and evidence of renal organ damage, has been recognized (11, 12). Patients with MGRS develop proteinuria and renal dysfunction without progressing to myeloma. It has become clear that in addition to the amount of M-protein, the quality of M-protein affects different parts of the kidney. Even small B-cell clones with small amounts of M-protein [i.e., dangerous small B cell clones (11)] damage various parts of the kidney. The preva-

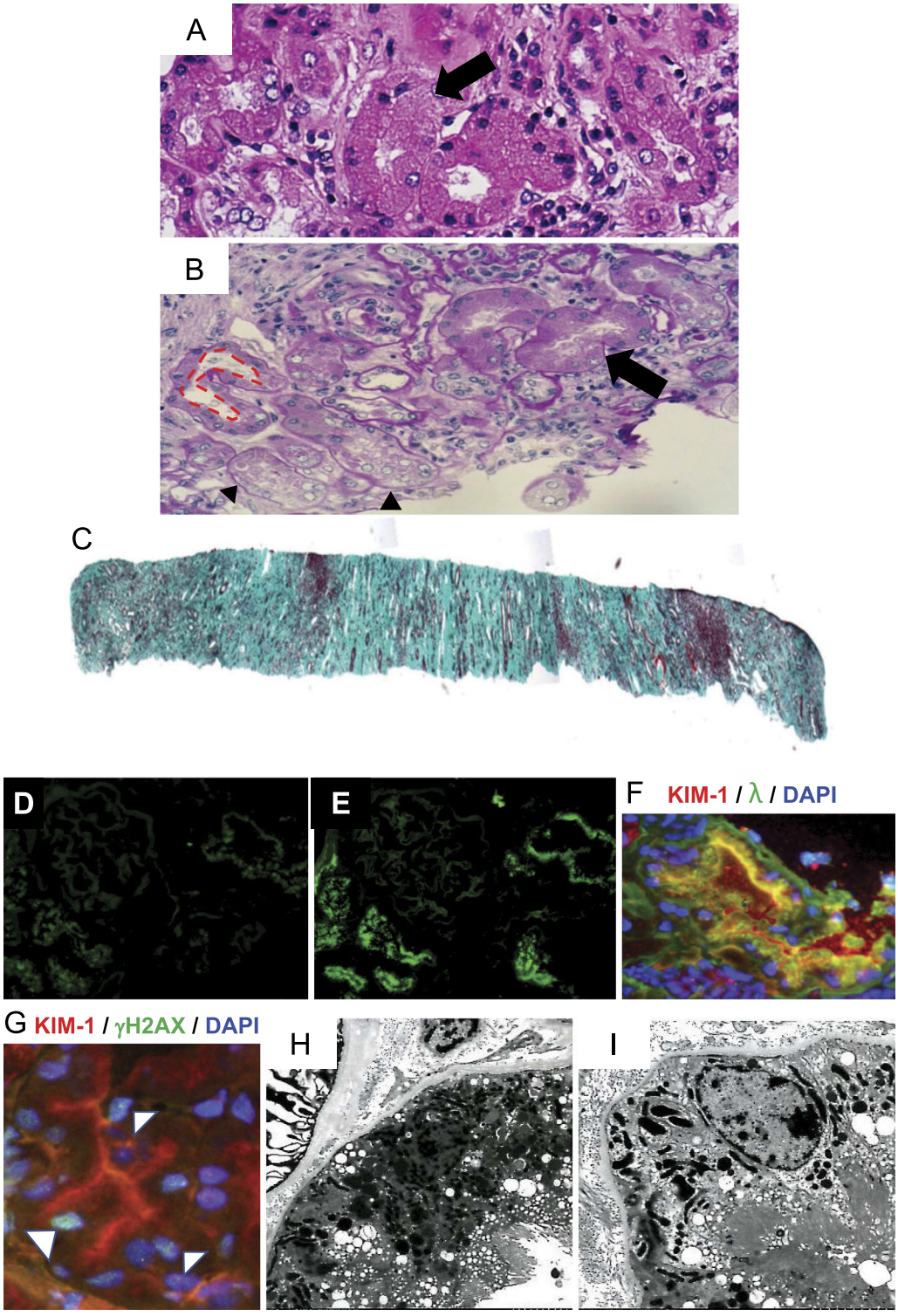

Figure 1. **The kidney biopsy findings: Hematoxylin and Eosin staining (A) and Periodic acid-Schiff staining showed (B) swelling (arrow), loss of brush boarder (surrounded by a dotted line) and detachment from the basement membrane (arrowhead) in the proximal tubular cells. (original magnification ×200). (C) Masson trichrome staining showed severe interstitial fibrosis (original magnification, ×40). (D, E) Immunofluorescence microscopy showed negative staining for κ light chains (D) and positive staining for λ light chains in the proximal tubules (E) (original magnification ×200). (F) Immunofluorescence microscopy showed that the λ light chain-positive proximal tubule became KIM-1 positive (original magnification, ×600). (G) Immunofluorescence microscopy showed DNA damage (arrowhead) in the KIM-1-positive injured proximal tubule (original magnification, ×600). (H, I) Electron microscopy revealed the absence of crystal formation in the proximal tubules. (original magnification, ×3,000 and ×4,000, respectively).**

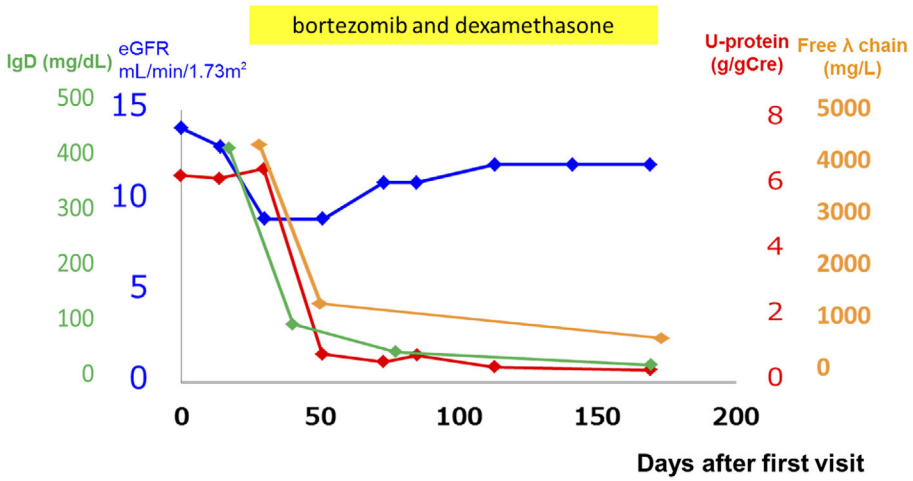

Figure 2. **The clinical course. eGFR (mL/min/1.73m^2), IgD (mg/dL), urine protein (g/gCre) and free λ light chains (mg/L) are shown in blue, green, red and orange lines, respectively. Days indicates the number of days after the first visit to our department.**

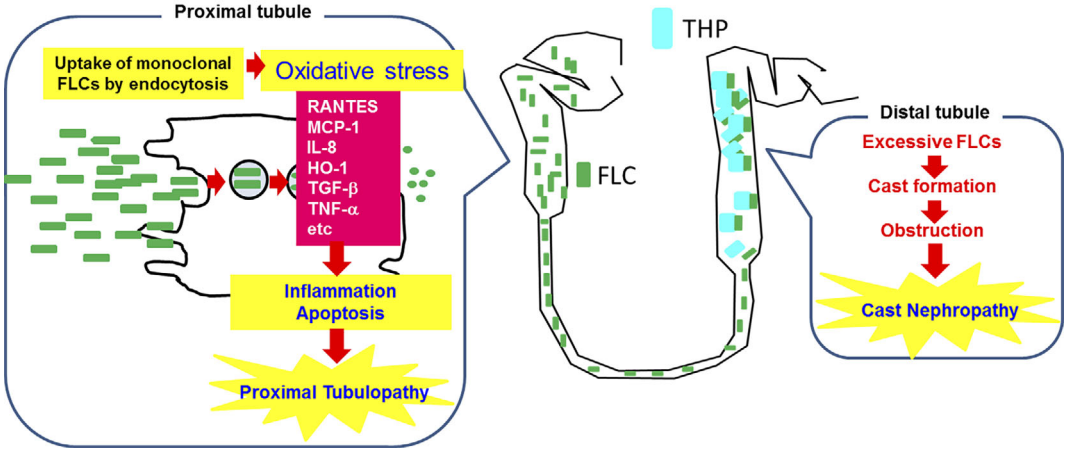

Figure 3. **The mechanism of free light chain-related tubular disease. THP: Tamm-Horsfall glycoprotein, FLCs: free light chains**

lence of MGRS and the prognosis of the kidney and survival after treatment remain to be clarified and studies have indicated the benefits of aggressive therapy in selected patients with LCPT (2). Future prospective clinical research studies are necessary (11, 12).

In summary, we herein described a case of light chain proximal tubulopathy, a rare form of paraprotein-related kidney disease in an elderly woman who presented with a loss of appetite and general fatigue. Treatment with bortezomib and dexamethasone led to a VGPR, without a worsening of her kidney function. The prevalence of chronic kidney disease (CKD) and plasma cell dyscrasia is high in the elderly. Because CKD will increase and be a greater burden in aging societies, it is important for physicians to consider paraprotein related kidney disease in the differential diagnosis of elderly patients with kidney dysfunction. An early diagnosis and treatment of paraprotein-related kidney disease can help to prevent end-stage renal failure.

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

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