Kidney Medicine

Concurrent Crystalline Light-Chain Proximal Tubulopathy and Membranous Nephropathy: A Case Report and Literature Review

Huizi Zhang, Chunyun Zhang, and Hua Su

Light-chain proximal tubulopathy (LCPT) is typically characterized by the intracytoplasmic deposition of light chains within the proximal tubular epithelial cells, which is usually classified into crystalline and noncrystalline subgroups. Membranous nephropathy (MN) is a common glomerular disease characterized by diffused subepithelial electron-dense deposits along the capillary loop accompanied by the effacement and microvillus transformation of the foot process. Here, we report a biopsy-confirmed case of a concurrence of LCPT with crystals (κ light chains restricted) and antigen-undetermined MN in a male patient. The patient presented with low-molecular-weight proteinuria, increased serum creatinine levels, and incomplete Fanconi syndrome. To our knowledge, this is the first report of a concurrence of LCPT and independent MN of unknown target antigens, which may enrich our recognition of monoclonal gammopathy of renal significance with synchronous MN.

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INTRODUCTION

Light-chain proximal tubulopathy (LCPT) is characterized by the intracellular accumulation of monoclonal light chains (LCs) within proximal tubules. Clinical manifestations include Fanconi syndrome, low-molecular-weight proteinuria, and progressive renal insufficiency.[1] LCPT is diagnosed based on a combination of multiple pathologic examinations, including conventional immunofluorescence (IF), protease-digested immunostaining, electron microscopy (EM), or even immunoelectron microscopy (IEM). As an early clue for hematologic diseases, timely diagnosis and appropriate management of LCPT are crucial.[2,3]

Membranous nephropathy (MN) is one of the most common pathologic types of nephrotic syndrome in adults.[4] However, the co-occurrence of LCPT with MN has not been reported. Here, we describe a novel case of LCPT and MN in a male patient.

CASE REPORT

A man in his 50s presented with a 4-year history of mild kidney dysfunction without any medical treatment. He denied a history of hypertension, diabetes, smoking, or alcohol intake. On admission, urinalysis revealed protein (2+) and glucose (2+). The total urine protein was 920 mg/24 h and urine albumin was 178.2 mg/24 h. Serologic analysis showed that the serum creatinine level was 1.38 mg/dL (reference range: 0.65-1.26) and the uric acid level was 2.05 mg/dL (reference range: 3.49-7.19). No abnormalities were found for hemoglobin, serum albumin, glucose, calcium ion, complements, autoimmune antibodies, and antiphospholipase A2 receptor (PLA2R) antibody. Tests for HIV, syphilis, hepatitis B and C virus, and tumor markers were negative. The serum free light-chain κ/λ ratio was 5.47 (the reference range for the decreased estimated glomerular filtration rate: 0.34-3.10 mL/min/1.73 m^2), and the test for urine Bence Jone protein was positive. A radiographic examination revealed no osteolytic lesions. Detailed examination results are summarized in Table S1. Bone marrow aspiration was conducted twice, and the results showed that the percentage of plasma cells was 3.5% and 6.5%, respectively. Based on these results, the patient was diagnosed with monoclonal gammopathy (MG) with chronic kidney disease.

A kidney biopsy was performed to elucidate the underlying cause of kidney dysfunction. IF on frozen tissues revealed the presence of fine granular deposits of IgG4 (2+) along a few glomerular capillary loops. However, staining for IgM, IgA, IgG1, IgG2, IgG3, C3, C4, C1q, PLA2R, and THSD7A was negative.

Light microscopy examined a total of 22 glomeruli, of which 2 were globally sclerotic. Among the nonsclerotic glomeruli, periodic acid–silver methenamine staining revealed the presence of glomerular basement membrane spikes (Fig 1 A). Furthermore, tubular epithelial cells exhibited focal vacuolization and cytoplasmic inclusions with peculiar morphology. A focal loss of the brush border with epithelial simplification and a small number of protein casts within the tubular lumen were observed (Fig 1B). Congo red staining for amyloid was negative.

EM revealed segmental thickening of the glomerular basement membrane, fused foot processes, scattered diffused subepithelial electron-dense deposits in the subepithelial domain with glomerular basement membrane reaction, and a few electron-dense deposits in the mesangium (Fig S1C and D). The tubular injury was evident with increased intracellular lysosomes and some rod-, rhomboid-, needled-, or irregular-shaped crystals (Fig 1E and F).

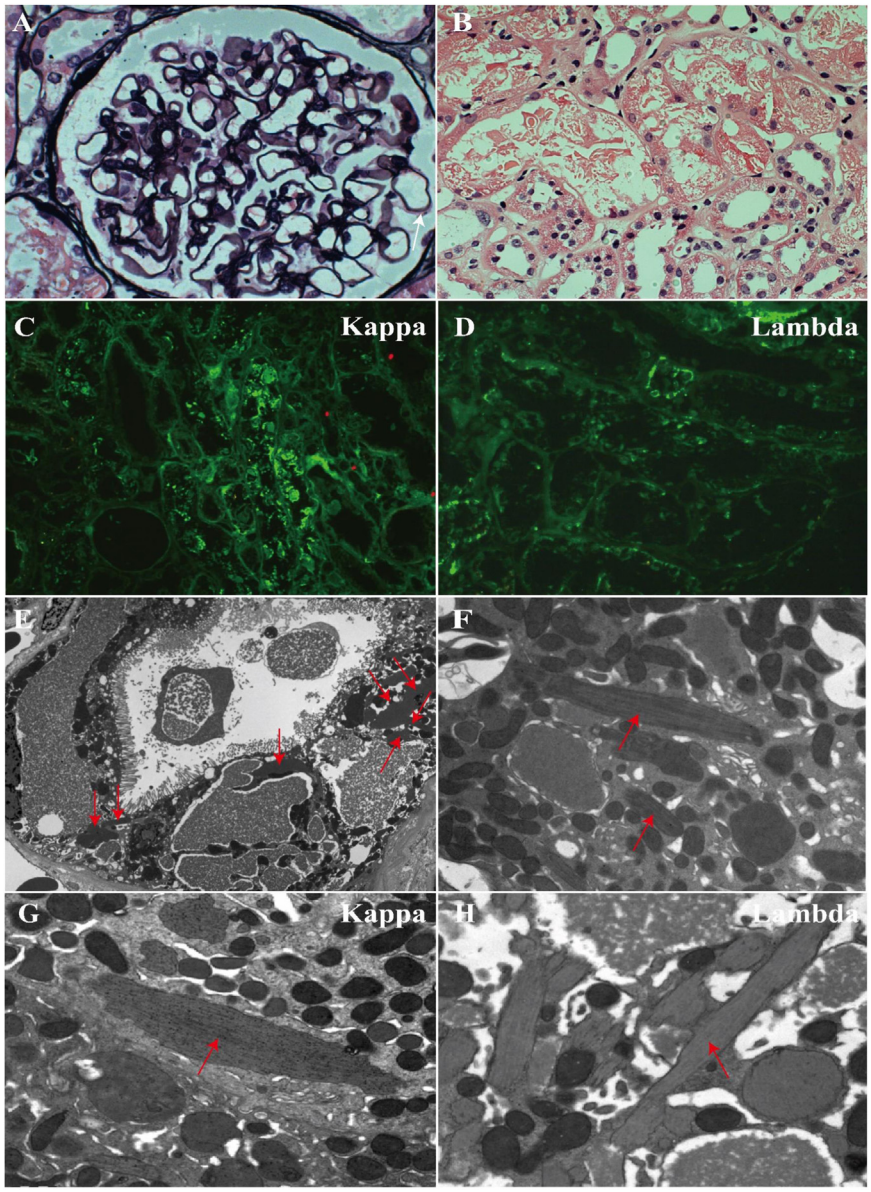

Figure 1. Kidney biopsy findings. (A) Stiff and dilated glomerular capillary loops and basement membrane "spikes" (white arrow) (periodic acid–silver methenamine stain) are shown under light microscopy. (B) The proximal tubular epithelial cells appear vacuolar and granular, with some peculiar substances in the cytoplasm (hematoxylin and eosin stain). (C, D) Positive staining of κ-LCs (3+) in the cytoplasm of some PTECs and negative staining of λ-LCs are shown using immunofluorescence microscopy of paraffin-embedded tissues. (E, F) Electron microscopy reveals the presence of some rod-, rhomboid-, needled-, or irregular-shaped crystals (red arrows) and increased intracellular lysosomes in the cytoplasm of PTECs. (G, H) Immunoelectron microscopy further highlights the rod- and diamond-shaped crystals (red arrows) in the cytoplasm of PTECs, which are positively stained for κ-LCs while negatively for λ-LCs using colloidal gold labeling. Original magnification: ×400 for panels A, B, C, and D; ×1,000 for panel E; ×5,000 for panel F; ×15,000 for panel G; and ×20,000 for panel H. Abbreviations: κ-LCs, kappa light chains; λ-LCs, lambda light chains; PTECs, proximal tubular epithelial cells.

Because the patient exhibited clinical symptoms of MG and the presence of peculiar substances in proximal tubular epithelial cells, further IF of paraffin-embedded tissues (IF-P) and IEM examinations were performed. IF-P exhibited restricted staining of κ-LCs (3+) in the cytoplasm of PTECs (Fig 1C) without any diagnostic staining of λ-LCs (Fig 1D). Meanwhile, neither κ- nor λ-LCs were detected in glomeruli (Fig S1A and B). Consistently, the colloidal gold labeling technique reconfirmed the aforementioned findings (Fig 1G and H; Fig S1E and F).

We performed mass spectroscopy (MS) by isolating glomeruli and tubules from the specimen to investigate the relationship between MG and MN further. No known MN-associated targeted antigens, including NEP, PLA2R,

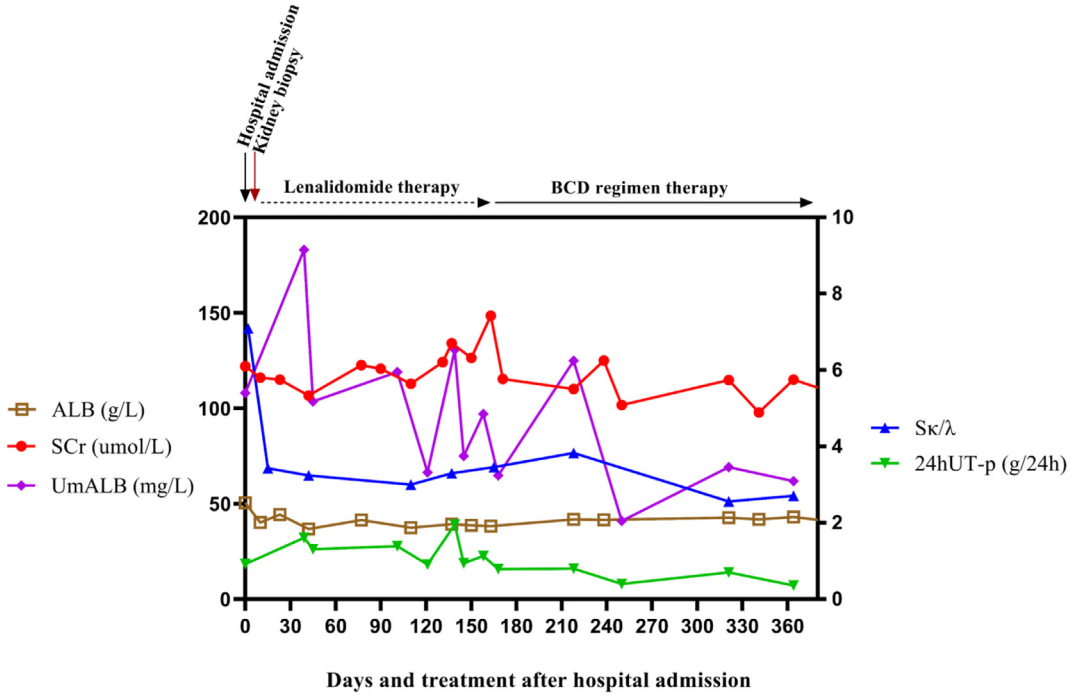

Figure 2. The clinical course and treatment outcome of the patient. After admission, the patient underwent a kidney biopsy on the fifth day. Subsequently, treatment was initiated with oral lenalidomide for a total of 6 courses, beginning on the 10th day of admission. Based on observed efficacy, the treatment was adjusted to a bortezomib-cyclophosphamide-dexamethasone regimen on day 165, and the patient underwent 4 courses of this regimen. The graph shows changes in kidney function, albumin, urine protein, and monoclonal immunoglobulin. The values for ALB (g/L), Scr (μmol/L), and UmALB (mg/L) are represented by the brown, red, and purple lines, respectively, on the left Y-axis. The values for Sκ/λ and 24-h UT-p are marked by the blue and green lines, respectively, on the right Y-axis. The timescale represents the number of days after the initial visit of the patient to the hospital. Conversion factors for units: Scr in mg/dL to μmol/L, ×88.4; UA in mg/dL to μmol/L, ×59.48. Abbreviations: ALB, albumin; BCD, bortezomib-cyclophosphamide-dexamethasone; Scr, serum creatinine; Sκ/λ, serum kappa/lambda; UmALB, urine microalbumin; 24-h UT-p, 24-hour urine total protein.

THSD7A, EXT1/2, NELL1, SEMA3B, PCDH7, NCAM1, HTRA1, CNTN1, TGBR3, FAT1, NTNG1, NDNF, and PCSK6, were detected in the glomeruli. Furthermore, no significant difference was observed in the glomerular expression of κ- and λ-LCs compared with that in a cohort of nearly 50 cases of immune complex–mediated glomerulonephritis. However, a substantially increased κ/λ ratio was found in the tubules. Along with the aforementioned observations, a diagnosis of LCPT (κ-LCs restricted) with concurrent MN was established.

After one course of lenalidomide treatment, bone marrow aspiration was performed for the third time, which revealed the presence of 3% of plasma cells, and biopsy revealed the presence of 5% of monoclonal proliferating plasma cells. After another 5 courses of lenalidomide, the fourth bone marrow aspiration revealed the presence of 1% of plasmacytoma cells, and the biopsy revealed the presence of 3% of monoclonal proliferating plasma cells. However, the serum free light-chain ratio (κ-LCs: 109 mg/L; λ-LCs: 20.6 mg/L; and κ/λ: 5.291) did not improve and serum creatinine levels increased slightly. Therefore, the treatment was changed to a bortezomib-cyclophosphamide-dexamethasone regimen, and the patient underwent 4 courses of bortezomib-cyclophosphamide-dexamethasone chemotherapy. After that, the patient exhibited stable serum creatinine levels and slightly decreased urine protein levels. The patient continued to be monitored closely (Fig 2).

DISCUSSION

In this case, the patient presented with mild renal insufficiency, low-molecular-weight proteinuria, and M proteinemia. However, the results of bone marrow aspiration, which was performed 4 times, did not meet the diagnostic criteria of multiple myeloma or any other hematologic malignancy.[5] Therefore, a clinical diagnosis of MG was established, but whether it has renal significance was uncertain.[5] Therefore, a kidney biopsy was performed. Interestingly, glomerular lesions were observed in routine morphologic evaluations presenting as segmental deposits of IgG4 along the glomerular capillary loops, thickened glomerular basement membranes with spikes, and electron-dense deposits in the subepithelial regions, which was consistent with the diagnosis of MN. However, no monoclonal features were found in routine

immunostaining. Ultrastructural examination revealed numerous rod- and rhombic-shaped crystals in the cytoplasm of PTECs. IF-P and IEM revealed restricted κ-LCs in the cytoplasm of PTECs without monoclonal evidence in glomeruli. MS analysis found no known MN-associated target antigens and monoclonal signs in glomeruli. Altogether, based on these morphologic and molecular findings, a final diagnosis of LCPT with crystals (κ-LCs restricted) with irrelevant and unknown etiology of MN was established. To our knowledge, this is the first reported case of concurrent LCPT with MN.

LCPT is histologically characterized by the presence of either crystalline or noncrystalline LCs in the cytoplasm of PTECs.[6] In LCPT with crystals, specific mutations in the variable domain of nonpolar residues of monoclonal immunoglobulin LCs, particularly within the Vκ1 subgroup, confer resistance to protein hydrolysis and promote self-aggregation and crystal formation. This impairs renal tubular reabsorption and ultimately leads to the loss of kidney function.[7-9] Noncrystalline LCPT can be caused by either κ-LCs or λ-LCs.[10,11] Compared to noncrystalline LCPT, patients with crystalline LCPT may experience more frequent Fanconi syndrome and severe proteinuria and kidney function impairment.[11] As one of the less prevalent manifestations of monoclonal gammopathy of renal significance, the diagnosis of LCPT is based on a comprehensive array of methodologies. In LCPT with crystals, routine IF on frozen tissues is often negative owing to the crystal structure of LCs blocking the antigen-antibody binding sites; thus, IF-P should be performed routinely when LCPT is highly suspected.[12,13] A previous study showed that IF-P exhibited better sensitivity than IF on frozen tissues, with values of 97% and 35%, respectively.[11] EM is also performed to observe the morphology of the crystals and the deposition sites within the kidney.[14] Lastly, IEM can further confirm the monoclonal nature of the crystals.[15] In this case, a combination of IF on frozen tissues, IF-P, EM, IEM, and MS was used, and the diagnosis of κ-LC–restricted crystalline LCPT with MN was established.

MN is traditionally classified as primary MN (patients without identifiable etiology) or secondary MN (patients with known etiologies, including autoimmune disease, infection, malignancy, and drug toxicity).[16] In this case, the patient clinically presented a low amount of albumin in urine, but the pathologic findings fulfilled the diagnostic criteria of MN although the epithelial deposits were scattered and segmental. Mild albuminuria may be owing to the sparse distribution of deposits.[17] The immunostaining of PLA2R and THSD7A was negative, and further MS analysis revealed no known MN-associated target antigens. Furthermore, immunostaining and MS showed no monoclonal evidence in glomeruli. It was challenging to categorize our case into primary MN or secondary MN definitively; therefore, we diagnosed him with MN of unknown antigens. Furthermore, no direct or concrete evidence supporting the relevance of MG and MN was found in this case.

The association between MG and MN is not extensively studied. A multicenter study from China revealed that negative staining for PLA2R and positive staining for IgG3 are more frequently associated with MG.[18] In an American study, 85.7% of patients with MN having LC deposition exhibited κ restriction.[19] A Japanese study revealed that monoclonal gammopathy of renal significance combined with MN could present with monoclonal IgM deposits, and rituximab treatment can be effective.[20] These studies suggested that patients with MN exhibiting a PLA2R-negative and single IgG subtype with LC restriction should be diligently screened for underlying lymphoproliferative disorders.

To summarize, we reported the case of a patient presenting with MG, incomplete Fanconi syndrome, and low-molecular-weight proteinuria, who was diagnosed with crystalline LCPT (κ-LCs restricted) with concurrent MN. The kidney function of the patient improved after appropriate treatment. This particular case not only enriches our understanding of monoclonal gammopathy of renal significance with other unrelated pathologic lesions but also teaches us how to integrate clinical, morphological, and molecular information to make a rational and informative diagnosis. Moreover, the pathologists should diligently examine all the compartments of nephron and images to avoid overlooking potential concomitant lesions.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. The kidney biopsy findings of glomerulus.

Item S1. Materials and methods.

Table S1. The examination results of the patient.

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