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Kidney Biopsy Teaching Case

Recurrent Light Chain Proximal Tubulopathy in a Kidney Allograft

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We describe a rare case of light chain proximal tubulopathy developing in a kidney transplant 12 months following transplantation. The patient was known to have a monoclonal gammopathy of undetermined significance (MGUS) for more than 15 years. A kidney biopsy done to determine the cause of decline in kidney transplant function showed light chain proximal tubulopathy characterized by numerous eosinophilic and fuchsinophilic granules in proximal tubular epithelial cells, which stained for κ light chains on pronase-based immunofluorescence studies. Electron microscopy confirmed the diagnosis and showed numerous amorphous and geometrically shaped inclusions in proximal tubular epithelial cells. Evaluation of free light chains revealed markedly elevated κ light chains and bone marrow biopsy showed 5% to 10% κ light chain–restricted plasma cells. Retrospective evaluation of the native kidney biopsy performed 15 years earlier also showed numerous fuchsinophilic granules in proximal tubules that stained brightly for κ light chains on pronase-based immunofluorescence studies. The patient was treated with a regimen of bortezomib and dexamethasone with good partial hematologic response and improvement of kidney function. To summarize, we describe a case of recurrent light chain proximal tubulopathy in the transplant, which is an unusual but important cause of decreased kidney function in the setting of a monoclonal gammopathy.

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INTRODUCTION

Light chain proximal tubulopathy is a very rare kidney disease defined by massive deposits of monoclonal light chains in the form of either crystals or amorphous deposits in cytoplasm of the epithelium of the proximal tubule.[1,2] It is part of a larger spectrum of lesions secondary to dysproteinemias known as immunoglobulin-related crystalline nephropathies. In the native kidney, light chain proximal tubulopathy accounts for approximately 0.5% to 5% of kidney diseases associated with paraproteinemia.[2,3] The prognosis of light chain proximal tubulopathy is difficult to predict and in part is likely related to the hematologic response of the dysproteinemia. Cases of light chain proximal tubulopathy are rare; there are only a few studies in native kidneys and even fewer of light chain proximal tubulopathy in the kidney transplant.[4,5]

We report a case of light chain proximal tubulopathy in a white woman diagnosed 12 months after kidney transplantation, secondary to the progression of long-standing immunoglobulin M κ light chain monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma. Review of the native kidney biopsy done 15 years earlier along with pronase-based immunofluorescence microscopy on the native kidney biopsy specimen also revealed light chain proximal tubulopathy. We describe this unusual case of recurrent light chain proximal tubulopathy in a kidney transplant that responded well following treatment of the multiple myeloma.

CASE REPORT

Case History and Initial Laboratory Data

A 67-year-old white woman who underwent living related kidney transplantation was referred in September 2015 for evaluation of declining kidney transplant function. The patient had initially presented in September 2000 with a creatinine level of 2 mg/dL, estimated glomerular filtration rate (eGFR) of 28 mL/min/1.73 m^2 by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, and proteinuria with protein excretion of 1.3 g/24 h. Kidney biopsy showed mild arterial sclerosis, mild focal global glomerulosclerosis, and mild tubular atrophy and interstitial fibrosis. Serum complement levels were within the reference ranges, and antineutrophil cytoplasmic antibody, antinuclear antibody, and hepatitis B and C serologic test results were negative. At the time, a monoclonal κ light chain was

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detected in urine on immunofixation studies. Additional medical history included hypertension, hyperlipidemia, obstructive sleep apnea, and nicotine dependence. No bone marrow biopsy was performed, and she was considered to have MGUS and was treated conservatively. Periodic evaluations of the monoclonal gammopathy showed no progression of the MGUS. In November 2012, serum creatinine level was 3.2 mg/dL, with eGFR of 15 mL/min/1.73 m^2.

Kidney function continued to deteriorate, and in February 2013, the patient received a preemptive living unrelated kidney transplant at another institution. The immediate posttransplantation course was unremarkable. Transplant immunosuppression was maintained with azathioprine, 150 mg, daily, and tacrolimus, 4 mg, orally twice daily. One year later, her creatinine level increased from a baseline of 1.4 to 2.6 mg/dL (eGFR, 39 to 19 mL/min/1.73 m^2), following which a kidney transplant biopsy was performed. Physical examination findings and vital signs were unremarkable. Urinalysis showed glycosuria, but mild proteinuria (protein excretion, 0.8 g of protein per gram of creatinine).

Kidney Biopsy 1

The specimen from the native kidney biopsy, which had been performed in December 2000, was retrieved and retrospectively analyzed. There was 1 core of kidney tissue containing cortex and medulla. There were 8 glomeruli present, of which 5 were globally sclerosed. Glomeruli displayed a mild increase in mesangial matrix, but proliferative features were not present. Proximal tubules were distended and filled with fuchsinophilic droplets that were periodic acid−Schiff and silver negative. There was only mild (10%) tubular atrophy and interstitial fibrosis present. Electron microscopy showed that proximal tubules were filled with numerous rectangular and geometrically shaped crystals, in a parallel array on higher magnification. Retrospective analysis by pronase-based immunofluorescence microscopy showed that the tubules were filled with droplets that stained brightly for κ light chains but were negative for λ light chains. Native kidney biopsy findings are shown in Fig 1.

Diagnosis 1

Light chain proximal tubulopathy.

Kidney Biopsy 2

The transplant kidney biopsy was performed in April 2014. Two cores of kidney tissue were present, containing 17 glomeruli, none of which were globally sclerosed. Glomeruli were unremarkable and showed no proliferative features. The mesangium was not expanded and nodule formation was not present. Proximal tubules were distended, and proximal tubular epithelial cells were filled with eosinophilic, intensely fuchsinophilic, periodic acid−Schiff and silver–negative droplets that had a crystalline appearance in some tubules. The material did not polarize under birefringent light. A single tubule contained a rectangular cast. There was no interstitial inflammation, and only mild (20%) tubular atrophy and interstitial fibrosis was present. Arteries showed mild arteriosclerosis. Immunofluorescence studies performed after pronase digestion of the paraffin-embedded material revealed numerous droplets within the proximal tubular epithelial cells that stained for κ light chains but were negative for λ light chains. Ultrastructural examination of a glomerulus showed well-preserved foot processes of visceral epithelial cells. Electron-dense or fibrillary deposits were not detected in the mesangium or along capillary walls. Tubules contained numerous inclusions in proximal tubules. In many tubules, the inclusions were within lysosomes. In others, crystalline inclusions were present free in the cytoplasm. The crystalline inclusions had geometrical shapes including rectangular, rhomboidal, and needle-shaped. Biopsy findings are shown in Fig 2.

Diagnosis 2

Light chain proximal tubulopathy, recurrent.

Clinical Follow-up

Laboratory evaluation of κ free light chains in serum showed elevated values of 50 to 60 (reference range, 0.33-1.94) mg/dL. The λ free light chains were within the reference range. Bone marrow biopsy showed features of multiple myeloma with 5% to 10% of plasma cells that were positive for monotypic κ light chains. Congo Red stain gave negative results. Imaging studies did not show evidence of lytic lesions. The patient received 4 cycles of bortezomib and dexamethasone, resulting in the decline in κ free light chains to 3.8 mg/dL, indicating a very good partial response. Since then, κ light chain levels have remained stable. Kidney function also improved, with serum creatinine levels decreasing progressively to 1.2 mg/dL (eGFR, 47 mL/min/1.73 m^2), which is consistent with baseline values. At last follow-up, kidney function remained stable (serum creatinine, 1.2 mg/dL; iothalamate clearance, 40 mL/min) and κ free light chains were 6.4 mg/dL. However, dipstick urinalysis continues to show normoglycemic glycosuria (glucose, 28 mg/dL) and specific gravity < 1.005. A repeat bone marrow biopsy showed 5% κ light chain−restricted plasma cells. In general, the patient is doing well, except for a generalized sensorimotor peripheral neuropathy likely secondary to bortezomib neurotoxicity that was documented with instrumental imaging, nerve conduction studies, electromyography, and nerve biopsy to exclude any neural disease related to multiple myeloma.

DISCUSSION

Monoclonal gammopathy, either in the setting of MGUS or monoclonal gammopathy of renal significance (MGUS/MGRS) or multiple myeloma, may result in a wide spectrum of kidney lesions.[6-9] In the past, kidney biopsy in patients with multiple myeloma and decreased kidney function was not routinely performed because it was considered unnecessary and invasive. However, it is now well recognized that the underlying kidney lesion needs to be defined for optimal treatment strategies and prognosis. In this teaching case, we illustrate a case of recurrent light chain proximal tubulopathy diagnosed in a kidney transplant.

The exact mechanisms of how proximal tubules are affected by this condition are not entirely clear, although a series of pathologic steps driven by the toxic circulating monoclonal light chain are likely responsible. Briefly, after filtration by glomeruli, light chains are captured in the proximal tubule by the megalin/cubilin system and processed in lysosomes for breakdown and recirculation of amino acids. This process is kept in check under physiologic conditions when low amounts of proteins escape the filtration barrier. In light chain proximal tubulopathy, the inability of the lysosomal enzyme cathepsin B to lyse the variable region of the large amounts of monoclonal light chains is considered the pathogenic defining event.[10] The persistence of light chains in the endolysosomal environment then results in either accumulation of crystalline material, which is usually