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Exceptional Case

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Amyloid proximal tubulopathy: a novel form of light chain proximal tubulopathy

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Abstract
Light chain proximal tubulopathy is a paraproteinemic-related kidney disease most commonly seen in patients with a plasma cell dyscrasia. The classic description is that of proximal tubules with kappa-restricted intracytoplasmic crystals in a patient with a clinical Fanconi's syndrome. Recently, other variants of light chain proximal tubulopathy have been described including those without crystal formation. We expand the morphologic spectrum in this report of a patient who presented with acute renal failure, proteinuria and hematuria. Biopsy revealed proximal tubulopathy in which the proximal tubules show intracytoplasmic amyloid formation. This is the first description, to our knowledge, of amyloid proximal tubulopathy.

Keywords: amyloid; kidney biopsy; light chain proximal tubulopathy; multiple myeloma

Background

Kidney disease is a common manifestation of multiple myeloma and the second leading cause of death in myeloma patients [1]. The most common paraprotein-related diseases of the kidney are amyloidosis, light chain deposition disease and light chain cast nephropathy. Less common forms of paraproteinemic disease in multiple myeloma include cryoglobulinemic glomerulonephritis and light chain proximal tubulopathy.

Light chain proximal tubulopathy is a form of proximal tubule injury secondary to increased filtration of pathogenic light chains. The classic and most widely recognized form of this disease has kappa-restricted intracytoplasmic crystals on renal biopsy and the clinical manifestation of a Fanconi's syndrome [2]. In recent years, the pathologic spectrum has been expanded to include cases with fibrillary cytoplasmic inclusions [3] and those showing light chain restriction within the lysosomes without inclusions [4].

AL amyloidosis deposition has been described in all compartments of the kidney and is frequently seen in the glomeruli, arterial walls and interstitium. Amyloid is seen in the tubular lumens in cases of light chain cast nephropathy when the casts prove to be Congo red positive [5]. We lengthen the list of possible locations for renal amyloid deposition and further expand the spectrum of lesions in light chain proximal tubulopathy in this report detailing the first description of amyloid proximal tubulopathy.

Case report

A 67-year-old Caucasian male presented for a routine checkup. Medications included lisinopril for hypertension and simvastatin for hyperlipidemia. The physical examination was unremarkable. When laboratory studies returned 2 days after the visit, the patient was called to the hospital for admission in order to evaluate an elevated serum creatinine (Cr) at 6.7 mg/dL (592.3 μmol/L) with an estimated glomerular filtration rate (GFR) of 8 mL/min/1.73m^2 (0.133 mL/s/1.73m^2).

Further questioning on admission revealed a 3- to 4-week history of fatigue and poor appetite as well as increased thirst and recent nocturia. He also reported taking occasional ibuprofen for mild back discomfort. He denied fever, chills, shortness of breath, nausea, vomiting and diarrhea. Physical examination was again unremarkable and vital signs were within normal limits. A repeat serum Cr at the time of admission was 8.5 mg/dL (751.4 μmol/L) with a GFR of 6 mL/min/1.73m^2 (0.100 mL/s/1.73m^2). He was also found to be hyperkalemic with a potassium level of 6.6 mEq/L (6.6 mmol/L) and to have mild thrombocytopenia with a platelet count of 137 $\times$ 10^3/μL (137 $\times$ 10^9/L). Urinalysis was positive for protein and showed moderate blood. A free lambda light chain was detected in the serum and urine by immunofixation. The remaining laboratory values were unremarkable with a normal hemoglobin and hematocrit at 14.1 g/dL (141 g/L) and 43.0%, respectively. The remaining electrolytes were within normal limits with sodium of 139 mEq/L (139 mmol/L), chloride of 106 mEq/L (106 mmol/L) and calcium of 9.2 mg/dL (2.3 mmol/L). He had normal liver function with alkaline phosphatase of 79 U/L, aspartate aminotransferase of 15 U/L, alanine aminotransferase of 15 U/L, total bilirubin of 0.3 mg/dL (5.1 μmol/L), albumin of 4.1 g/dL (41 g/L) and normal coagulation studies with a prothrombin time of 13.6 s and an International Normalized Ratio of 1.05. Serologies for anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies and anti-glomerular basement membrane antibodies were negative. The urine

was negative for eosinophils. Renal ultrasound revealed symmetric kidneys that were normal in size with no hydronephrosis and renal cortical echotexture within normal limits.

A renal biopsy was performed. Ten glomeruli were available for light microscopic evaluation and all were unremarkable. There was severe tubular injury with tubular nuclei showing prominent nucleoli and the proximal tubular cytoplasm showed frequent thinning with loss of the apical brush border. Approximately 30% of the proximal tubules had small round amorphous intracytoplasmic bodies. These bodies were periodic acid-Schiff negative, slightly silver positive and blue on trichrome stain. A Congo red stain was positive in these intracellular bodies and showed green birefringence upon polarization (Figure 1A and B). Congo red was negative throughout the remaining tissue including glomeruli, tubular lumens, arterial walls and interstitium.

One core of renal cortex was submitted for immunofluorescence evaluation. Sections were stained for IgA, IgG, IgM, C3, C4, C1q, fibrinogen, albumin, kappa and lambda light chains. All stains were negative within the six intact glomeruli. There was 3+ staining for lambda within the proximal tubule cytoplasm protein resorption droplets and focal tubules had larger inclusions corresponding to the size of the Congo red-positive bodies, which showed 2+ staining by lambda. Kappa was negative within the tubular cytoplasm (Figure 1C). The tubular casts stained equally with kappa and lambda. The tubular basement membranes were negative by kappa and lambda.

Electron microscopy was performed on a section of renal cortex. The evaluated glomerulus was unremarkable. There were no deposits in the glomerulus or along the tubular basement membranes. Glomerular epithelial foot processes were intact. Focal proximal tubules had intracytoplasmic aggregates of small, non-branching overlapping fibrils with a surrounding membrane (Figure 1D). These fibrils had a mean diameter of 9 nm. The renal biopsy was diagnosed as lambda light chain proximal tubulopathy consistent with amyloid proximal tubulopathy.

The results of the kidney biopsy prompted the clinical evaluation for multiple myeloma. A bone marrow biopsy was performed and showed increased cellularity largely consisting of atypical plasma cells. The overall cellularity was 95%, ~90% of which consisted of plasma cells. Immunoperoxidase stains demonstrated lambda restriction within these plasma cells. A Congo red stain was performed on the bone marrow tissue and was negative. The bone marrow

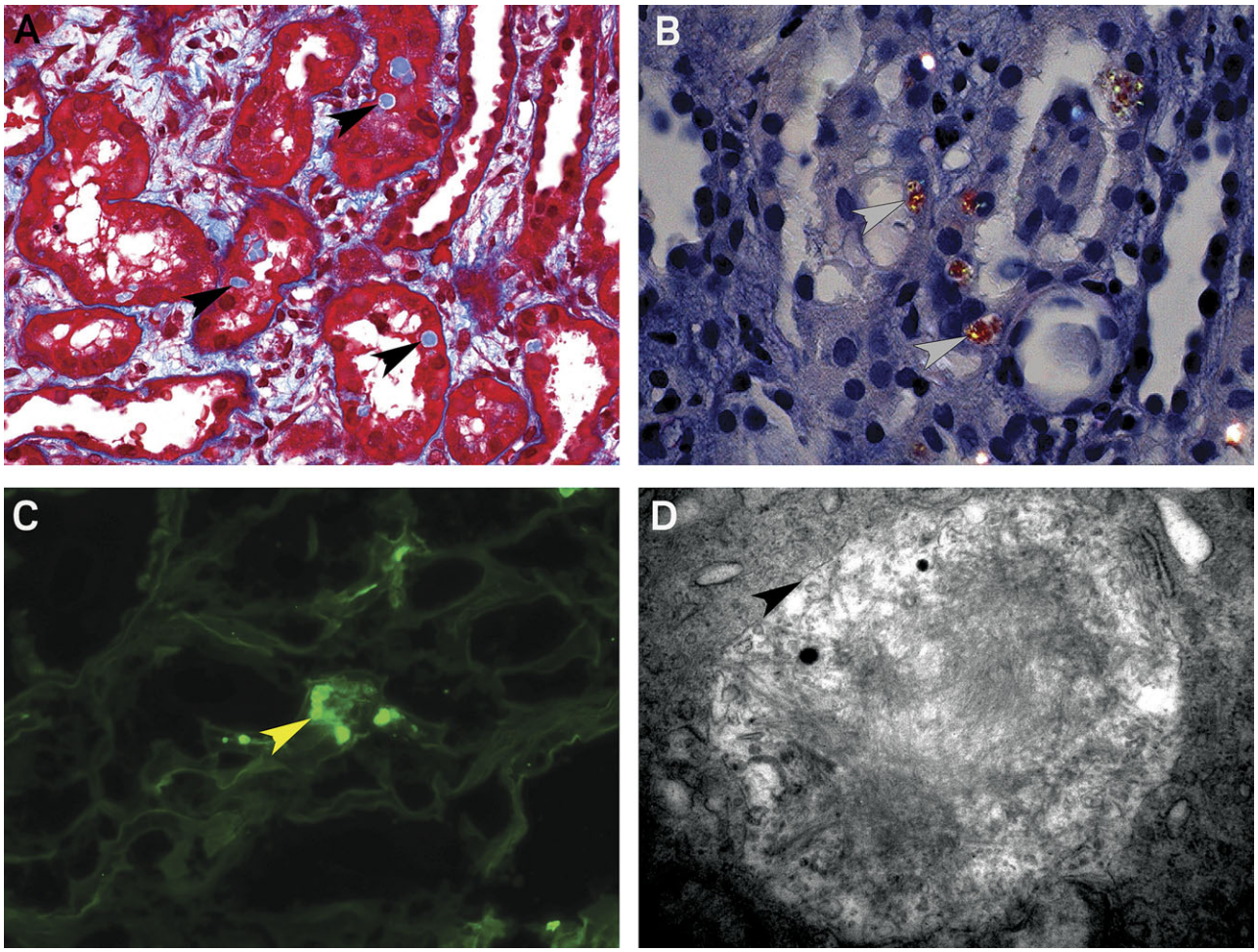

Fig. 1. Amyloid proximal tubulopathy. (**A**) Proximal tubules with intracytoplasmic inclusions (arrowheads) that stain blue on Masson's trichrome stain (original magnification ×400). (**B**) The inclusions (arrowheads) show green birefringence under polarized light on Congo red stain (original magnification ×600). (**C**) There is lambda restriction present in the proximal tubular cytoplasm inclusions (arrowhead) (fluorescein-conjugated anti-human lambda; original magnification ×400). (**D**) Transmission electron photomicrographs showing intracytoplasmic inclusion in the proximal tubule cytoplasm which appears to be membrane bound (arrowhead) and are composed of overlapping fibrils (unstained; original magnification ×35 000).

biopsy was diagnosed as plasma cell myeloma. A skeletal survey was performed and did not reveal any lesions in the bones.

The patient was treated after diagnosis with plasmapheresis to decrease his light chain burden and bortezomib 1.3 mg/m^2/dose along with oral dexamethasone 40 mg weekly for his multiple myeloma while hospitalized. He was discharged on hospital Day 24 with a serum Cr of 2.4 mg/dL (212.2 μmol/L) and a GFR of 27 mL/min/1.73m^2 (0.450 mL/s/1.73m^2). As an outpatient, lenalidomide 10 mg, 2 weeks on and 1 week off, was added to his treatment. His 4-month follow-up serum Cr was 3.8 mg/dL (335.9 μmol/L) with a GFR of 19 mL/min/1.73m^2 (0.317 mL/s/1.73m^2).

Discussion

AL Amyloidosis frequently involves the kidney and is diagnosed on renal biopsy. On biopsy, the predominant site of deposition is the glomerulus with lesser involvement of the interstitium and vessels [6]. Amyloid can also rarely be seen in the tubular lumens in amyloid cast nephropathy [5]. This is the first report, to our knowledge, of amyloid isolated to the proximal tubule cytoplasm.

Light chain proximal tubulopathy is a disease in which the proximal tubules are injured as a result of exposure to excess free light chains. The classic morphological description is that of kappa-restricted crystals in the proximal tubule cytoplasm. However, in one case series, light chain proximal tubulopathy without crystal formation was three times more common than cases with crystals [7]. Crystallization is clearly not necessary for light chains to cause injury to the renal tubular epithelium. The free light chains themselves have been shown to be pathogenic to renal proximal tubular cells both *in vitro* and *in vivo* [8–10]. Therefore, the acute tubular injury in our patient is explained by the tubulopathic nature of human free light chains.

This is the first reported case of light chain proximal tubulopathy with intracytoplasmic amyloid formation. It is also the first description, to our knowledge, of intracellular AL amyloidosis. It is not known whether this lesion indicates an increased risk of systemic involvement by amyloidosis. Our patient had no evidence of systemic amyloidosis with no amyloid on bone marrow biopsy, normal liver function and no involvement of other compartments of the kidney. We believe this lesion is best termed 'amyloid proximal tubulopathy' and should be considered a part of the broadening spectrum of light chain proximal tubulopathy. It is likely a rare form of the disease as we have seen 21 cases of isolated proximal tubulopathy in our laboratory over the past 3 years (13 of which were reported in a previous publication [7]) and this is the only case with intracytoplasmic amyloid formation.

Conflict of interest statement. None declared.

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