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Kidney Biopsy Teaching Case

Renal Amyloidosis Associated With a Novel Sequence Variant of Gelsolin

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We present a case of a 75-year-old woman who presented with progressive kidney failure. Kidney biopsy performed to determine the cause of kidney failure showed amyloidosis of undetermined type. Laser microdissection of the Congo Red–positive glomeruli followed by mass spectrometry studies showed a large number of spectra matching apolipoprotein E, serum amyloid P component, and gelsolin, consistent with a diagnosis of gelsolin-associated renal amyloidosis. Sequencing of the gelsolin gene revealed a previously undescribed sequence variant, a guanine to adenine substitution at nucleotide 580 of the coding sequence, corresponding to a predicted glycine to arginine mutation at amino acid 194. Gelsolin amyloidosis typically involves the nerves and skin, with only rare reported involvement of the kidney. An atypical finding on electron microscopy was that of a swirling pattern of the amyloid fibrils. The novel gelsolin variant may be responsible for the unusual clinical and pathologic presentation. The report also highlights the usefulness of laser microdissection and mass spectrometry in the typing of difficult cases of amyloidosis.
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INDEX WORDS: Amyloidosis; gelsolin amyloidosis; proteomics; gelsolin mutation; mass spectrometry.

INTRODUCTION

Amyloidosis is caused by extracellular deposition of proteins in an insoluble β-pleated format. Amyloid deposits are identified based on their apple-green birefringence under a polarized light microscope on Congo Red stain and by the presence of rigid nonbranching fibrils that measure 7.5-10 nm in diameter on electron microscopy.[1,2] The most common forms of systemic amyloidosis are immunoglobulin light chain amyloidosis and reactive secondary amyloidosis due to chronic inflammatory diseases (eg, rheumatoid arthritis and chronic infections).[3,4] New forms of amyloidosis, including hereditary and familial amyloidosis, are another group of amyloid that is now being diagnosed with increasing frequency. These include amyloid derived from transthyretins, fibrinogen α chain, lysozyme, and apolipoproteins.[3,5-8]

In this article, we describe an uncommon type of renal amyloidosis associated with accumulation of gelsolin, which shows some features not typical of renal amyloidosis. We describe the clinical and pathologic findings of gelsolin-associated renal amyloidosis. Furthermore, genetic analyses revealed a novel gelsolin mutation.

CASE REPORT

Case History and Laboratory Data

A 75-year-old white woman presented with chronic kidney disease and anemia. Her medical history was significant for hypertension, rheumatoid arthritis, and gout. She was being treated with an angiotensin-converting enzyme inhibitor and her blood pressure had been fairly well controlled over the years, with a reading of 144/70 mm Hg at presentation. Other medications included allopurinol, fenofibrate, ferrous sulfate, and tramadol. Her family history was unremarkable for kidney disease. Examination of the eyes showed full extraocular movements and no evidence of nystagmus or strabismus. The neck was supple with no evidence of lymphadenopathy or thyromegaly. Examinations of the chest, abdomen, and neurologic system were unremarkable, and extremities showed no edema. Initial laboratory findings included serum creatinine level of 3.8 mg/dL with an estimated glomerular filtration rate of 12 mL/min/1.73 m^2 by the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation. Urinalysis showed minimal proteinuria with 24-hour urinary protein excretion of 133 mg. No red blood cells or casts were present. Laboratory values are listed in Table 1. The initial impression was chronic kidney disease due to long-standing hypertension. Further evaluation showed a small κ spike on both serum and urine immunofixation electrophoresis. Given the progressive and somewhat rapid increase in serum creatinine level, a kidney biopsy was performed to rule out light chain disease or some other form of paraprotein-related kidney disease.

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Table 1. Laboratory Evaluation

	Laboratory Results	Reference Range
Hemoglobin (g/dL)	9.5	14-18.0
Hematocrit (%)	30.3	34.9-44.5
Platelets ($\times 10^3/\mu L$)	324	150-400
WBC count ($\times 10^9$/L)	6.4	3.5-10.5
Sedimentation rate (mm/h)	75	0-20
Uric acid (mg/dL)	8.2	3.5-7.2
Ferritin (μg/L)	181	13-150
Iron-binding saturation (%)	16	20-55
Total protein (g/dL)	7.2	6.3-7.9
Serum urea nitrogen (mg/dL)	47	4-20
Creatinine (mg/dL)	3.8	0.64-1.2
eGFR (mL/min/1.73 m^2)	12	>60
Glucose (mg/dL)	97	70-139
Calcium (mg/dL)	9.6	8.5-10.5
Urinalysis	Unremarkable	
Urinary protein/24 h (mg/24 h)	133	
Urine immunoelectrophoresis	Small monoclonal κ spike	
Serum immunoelectrophoresis	Small biclonal gammopathy IgA κ and IgG κ	

Note: Conversion factors for units: uric acid in mg/dL to umol/L, $\times$59.48; creatinine in mg/dL to umol/L, $\times$88.4; glucose in mg/dL to mmol/L, $\times$0.05551; calcium in mg/dL to mmol/L, $\times$0.2495.

Abbreviations: eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; WBC, white blood cell.

Kidney Biopsy

There were 2 cores of kidney tissue, comprising both cortex and medulla. There were 10 glomeruli present, of which 4 were globally sclerosed. Glomeruli showed mesangial expansion with weakly positive periodic acid–Schiff staining and silver-negative material (Fig 1A-B). Glomeruli did not show evidence of fibrinoid necrosis or crescent formation. Glomerular basement membranes appeared thickened, but did not show spikes or pinholes along the capillary walls. Approximately 10%-20% of the interstitium showed tubular atrophy and interstitial fibrosis. Arteries showed mild sclerosis of the vessel walls. Immunofluorescence studies were negative for immune deposits, although segmental granular mesangial deposition of C3 (2+) was noted. Electron microscopy showed accumulation of fibrillary deposits in the mesangium and capillary walls. In most areas, the deposits were not random, but were arranged in parallel arrays that showed a swirling pattern (Fig 2). Fibrils measured 9.6 nm in thickness. Deposits were not present in the interstitium or vessels. Congo Red staining performed at this time gave positive results, with reddish-brown material in the mesangium that showed birefringence under polarized light (Fig 1C and D).

The initial diagnosis was amyloidosis of undetermined origin, based on positive Congo Red stain with birefringence under polarized light and electron microscopy showing 9.6-mm-wide fibrillary deposits. The kidney biopsy findings were unusual in that electron microscopy studies showed organized deposits, which is not typical for amyloidosis. Clinically, the patient had minimal proteinuria, which also is unusual for glomerular amyloidosis. It was unlikely that the deposits represented fibrillary glomerulonephritis because immunofluorescence microscopy was clearly negative for immunoglobulins, including κ and λ light chains.

Laser Microdissection and Mass Spectrometry

To determine the protein composition of the fibrillary deposits, we performed laser microdissection (LMD) and mass spectrometry (MS) analysis of the glomeruli as previously described.[9,10] Briefly, glomeruli were microdissected from 2 samples by using laser capture techniques and digested with trypsin. The resulting peptides were subjected to liquid chromatography and tandem MS (LC-MS/MS), which showed a large number of spectra matching apolipoprotein E, serum amyloid P component, and gelsolin (Fig 3A and B). The presence of numerous spectra for apolipoprotein E and serum amyloid P component is consistent with the diagnosis of amyloidosis. LC-MS/MS also showed 24 and 30

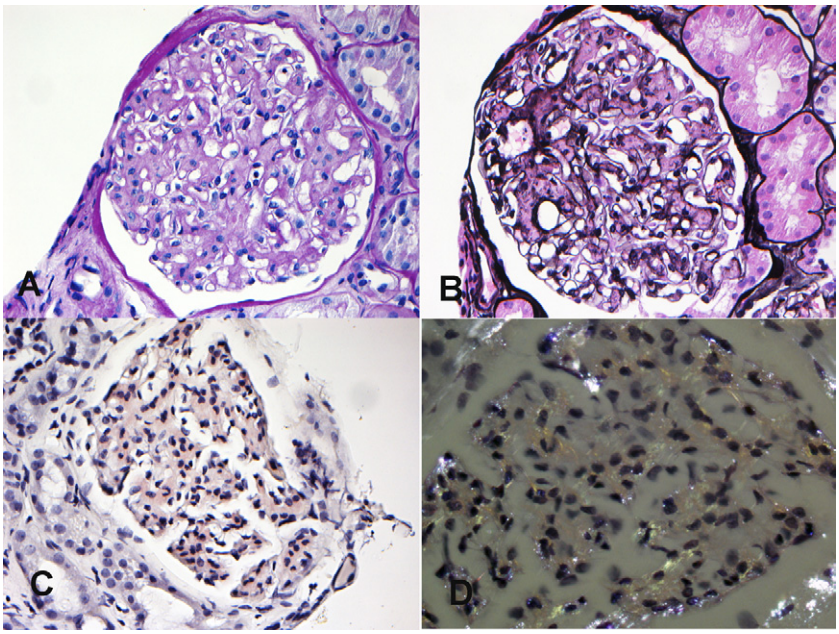

Figure 1. (A-B) Light microscopy shows mesangial expansion with weakly positive periodic acid–Schiff (PAS) material and silver-negative material. Congo Red–stained material is evident (C) under nonpolarized light and (D) generates apple-green birefringence under polarized light ([A] PAS; [B] silver-methanamine; [C-D] Congo Red; [A-D] original magnification, $\times$40).