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Case Report

Leukocyte Cell-Derived Chemotaxin 2-Associated Renal Amyloidosis: A Case Report

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ALECT2 · Amyloidosis · Chronic kidney disease · Tubulointerstitial nephritis

Abstract
Amyloidosis is a disorder characterized by the deposition of abnormal protein fibrils in tissues. Leukocyte cell-derived chemotaxin 2-associated amyloidosis is a recently recognized entity and is characterized by a distinctive clinicopathologic type of amyloid deposition manifested in adults by varying degrees of impaired kidney function and proteinuria. There are only a limited number of cases reported in the literature. We present a 64-year-old Hispanic female with a history of hypertension who was referred for chronic kidney disease management. The review of her laboratory tests revealed a serum creatinine of 1.5–1.8 mg/dL and microalbuminuria (in the presence of a bland urine sediment) in the past year. She denied any history of diabetes, rheumatologic disorders or exposure to intravenous contrast, nonsteroidal anti-inflammatory drugs, herbals, and heavy metals. Serological workup was negative. A renal biopsy showed diffuse infiltration of glomerulus with pale eosinophilic material strongly positive for Congo red stain and a similar eosinophilic material in the interstitium, muscular arteries, and arterioles. Electron microscopy showed marked infiltration of the mesangium, capillary loops, and interstitium with haphazardly arranged fibrillary deposits

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(9.8 nm thick). Liquid chromatography tandem mass spectrometry confirmed leukocyte cell-derived chemotaxin 2 (LECT2) amyloid deposition. LECT2 amyloidosis (ALECT2) should be suspected in renal biopsy specimens exhibiting extensive and strong mesangial as well as interstitial congophilia. Individuals with LECT2 renal amyloidosis have a varying prognosis. Therapeutic options include supportive measures and consideration of a kidney transplant for those with end-stage renal disease.

Introduction

Amyloidosis is a disorder characterized by the abnormal deposition of insoluble protein fibrils in tissues [1]. So far there have been more than 30 different types of amyloid protein discovered in humans [2]. The most recently described form of amyloidosis is derived from leukocyte cell-derived chemotaxin 2 (LECT2) [3]. It is one of the most common types of renal amyloidosis (2.7–10%) in the United States especially the southwestern United States [3]. It is an emerging disease that is beginning to be recognized as an important cause of end-stage renal disease (ESRD). Here we describe the case of a patient with LECT2 amyloidosis and illustrate the features of the ALECT2 that make it stand out among other forms of amyloidosis.

Case Report

A 64-year-old Hispanic female was referred to the Nephrology Clinic for evaluation of chronic kidney disease management. She denied any history of hematuria, dysuria, swelling of her extremities, joint pain, rash, cough, or hemoptysis. Her past medical history was significant only for hypertension. There was no history of diabetes, rheumatological disorders, exposure to intravenous contrast, nonsteroidal anti-inflammatory drugs, herbals, and heavy metals. Her home medications included amlodipine and over-the-counter multivitamins. Physical examination was unremarkable except for a blood pressure of 140/90 mm Hg. A review of laboratory tests revealed a serum creatinine (Cr) of 1.5–1.8 mg/dL in the past year. A comprehensive laboratory evaluation was done, which is shown in Table 1. Serum and urine electrophoresis was negative for monoclonal proteins. Serologies including the hepatitis panel, antineutrophil cytoplasmic antibodies, antinuclear antibody, anti-double-stranded DNA antibody, and complements were within the normal range. A renal ultrasound showed hyperechoic kidneys 11.2 cm in size on the right and 10.8 cm on the left. There was no hydronephrosis. A renal biopsy was performed. Light microscopy showed diffuse infiltration of glomerulus with pale eosinophilic material strongly positive for the Congo red stain. A similar eosinophilic material was present throughout the interstitium, muscular arteries, and arterioles (Fig. 1, Fig. 2). The immunofluorescence study was negative. Electron microscopy showed marked infiltration of mesangium, capillary loops, and interstitium with haphazardly arranged fibrillary deposits of an average thickness of 9.8 nm (Fig. 3). Liquid chromatography tandem mass spectrometry was performed on peptides extracted from Congo red-positive, microdissected areas of the paraffin-embedded kidney specimen. This revealed

LECT2-type amyloid deposition. The final diagnosis was renal amyloidosis due to LECT2 amyloid deposition. An echocardiogram and ultrasound of the abdomen revealed a normal heart and liver, respectively. A conservative line of approach was adopted. Antihypertensive treatment was switched to an angiotensin-converting enzyme inhibitor. Standard measures for chronic kidney management were adopted. One year after diagnosis Cr has remained stable around 1.6 mg/dL.

Discussion

Ever since the first case of ALECT2 was discovered by Benson et al. [4] in 2008, several cases have been reported including two case series. ALECT2 affects patients mainly of Hispanic origin especially Mexican Americans [5]. Other ethnicities with high prevalence include Arabs, Israelis, native Americans, Canadian aboriginees, Punjabis, and Sudanese people. It is less common in African Americans and Caucasians [6, 7]. Clinical features of patients with ALECT2 based on the various case series is presented in Table 2 [2, 7–10].

The pathogenesis of this disease is related to accumulation of a protein called LECT2 which was first isolated by Yamagoe et al. [11] in 1998. LECT2 protein is a multifunctional factor involved in chemotaxis, inflammation, immunomodulation, and the damage/repair process. Though synthesized mainly by hepatocytes, it is also expressed in a variety of other cells in many organs, including vascular endothelial cells, smooth muscle cells, adipocytes, and epithelial cells such as renal tubular epithelial cells [9]. Based on protein concentration estimates, systemic overexpression of LECT2 does not seem to be responsible for pathogenesis of ALECT2 [12]. Rather it is thought be due to the increased propensity of this protein to become amyloidogenic. Whether this increased propensity is due to genetic or nongenetic causes is not known at this point. According to the literature, ALECT2 involves G/A polymorphism affecting nucleotide 172 in exon 3 of the LECT2 protein that accounts for the presence of valine (in the place of isoleucine) at position 40 in the mature protein, and this substitution of the isoleucine with valine makes the protein unstable imparting an amyloidogenic property to the LECT2 protein [12]. Alternately Benson et al. [4] and Murphy et al. [9] proposed that the disease could be due to interference in the LECT2 catabolic pathway or LECT2 transport, possibly resulting from a genetic defect which ultimately results in an increased local tissue concentration of LECT2 leading to amyloid fibril formation.

The kidney is the primary target of this disease. Other common organs involved other than the kidney include liver, spleen, prostate, gastrointestinal tract, peripheral nervous system, and lungs [2, 13]. Cardiac involvement never occurs, which gives this disease a survival advantage compared to other forms of amyloidosis. Other organs which are not involved include brain, pancreas, and fibroadipose tissue [2]. A biopsy of the kidney or liver is the easiest way to confirm this diagnosis [14]. ALECT2 is characterized by the deposition of LECT2 protein in the interstitium, especially the cortical interstitium of the kidney. Because of the restriction to the interstitium, the amyloid could be missed histologically unless Congo red staining is routinely performed (the amyloid staining is strongly congophilic). Other amyloidoses with predominant interstitial involvement include apolipoprotein A1 and transthyretin-related amyloidosis [15]. There are varying degrees of glomerular and vascular involvement. In the study by Said et al. [10] glomerular involvement was seen in 91.7% and

vascular involvement in 84.3% whereas in the study by Larsen et al. [8], the figures were 88 and 83%, respectively. The most common glomerular involvement was mesangial expansion. On electron microscopy LECT2 protein will appear as randomly arranged fibrils with a diameter of 7–12 nm. In addition to the renal biopsy findings, confirmation of ALECT2 diagnosis requires immunohistochemistry or chemical analysis of the formalin-fixed paraffin-embedded tissue by tandem mass spectrometry [9].

LECT2 protein being a proinflammatory as well as a chemotactic agent seems to induce tubulointerstitial inflammation similar to the pathogenesis of chronic tubulointerstitial nephritis from infections, metabolic disorders, exposure to heavy metals, or hereditary diseases [16]. The LECT2 protein might be acting as the initiator and promotor of inflammation in the tubulointerstitium [17]. This unstable protein, which is also a cytokine, recruits mononuclear cells including macrophages and lymphocytes to the tubulointerstitium [12, 17]. This localized inflammatory process leads to further synthesis of the potentially amyloidogenic valine 40-containing LECT2 variant in individuals homozygous for the G allele. Since the underlying etiology is persistent and cannot be eliminated, it leads to chronic tubulointerstitial injury including the development of interstitial fibrosis and tubular atrophy.

Although the pathogenesis of ALECT2 is distinct from most other forms of amyloidosis, there seem to be some similarities to that of SAA amyloidosis. Like ALECT2, SAA is synthesized in the liver. Both have proinflammatory as well as chemotactic properties. This similarity in the expression of SAA and LECT2 protein has been described in patients with rheumatoid arthritis (RA). Both SAA and ALECT2 have been demonstrated in synovial fluid-derived mononuclear cells in RA patients [18]. Similarly, polymorphisms of SAA and LECT2 have been found to be associated with a risk of amyloidosis in RA [19, 20]. Finally, the primary target of both SAA amyloidosis and ALECT2 is the kidney. All these observations favor the fact that there might be a common pathway in the pathogenesis of SAA and alect2 amyloidosis. This might be important from the treatment standpoint and help in the development of new treatment options for ALECT2.

Most patients with ALECT2 present with minimal proteinuria, bland urine sediment and impaired renal function, and the diagnosis of ALECT2 is usually incidental following biopsies for unrelated conditions or uncertain diagnoses [21]. ALECT2 is a slowly progressive disease likely due to the selective involvement of the interstitium. Consequent to the uniqueness in histological and clinical presentation, ALECT2 has a variable short-term prognosis. The estimated mean rate of the decrease of estimated glomerular filtration rate is around 0.5 mL/min/1.73 m^2/month. Larger studies have shown a progression to ESRD in the range of 27–39% (Table 2). According to Said et al. [10] the projected median renal survival is 62 months. Factors which predicted a progression to ESRD include glomerulosclerosis, arteriosclerosis, the presence of comorbidities such as diabetes, concurrent disease on renal biopsy, and an initial Cr of more than 2 mg/dL. A full nephrotic syndrome is uncommon in renal ALECT2, which was present in only 10% of the patients in the series by Said et al. Neither the renal function nor the proteinuria correlates with the amyloid load in the renal biopsy.

There is no specific therapy for ALECT2. Transplantation remains the only effective treatment. But there is a high risk of recurrence in view of ongoing synthesis of the abnormal protein by the liver. Some potential future therapies for ALECT2 amyloidosis include reducing the supply of LECT2 (such as by Wnt/b-catinin signaling pathway inhibitors, etinoids, exisulind, and endostatin), inhibiting fibrillogenesis (such as by blocking the binding of gly-

cosaminoglycans to amyloid fibrils), enhancing the clearance of amyloid by immunotherapy, and promoting amyloid regression [3].

Statement of Ethics

Each author explicitly confirms that the manuscript meets the highest ethical standards for authors.

Disclosure Statement

None of the authors of this manuscript report any conflicts of interest.

Author Contributions

The authors state that this paper has not been published previously and is not currently being assessed for publication by another journal. Each author has contributed substantially to the preparation and production of the paper and approves of its submission to the journal.

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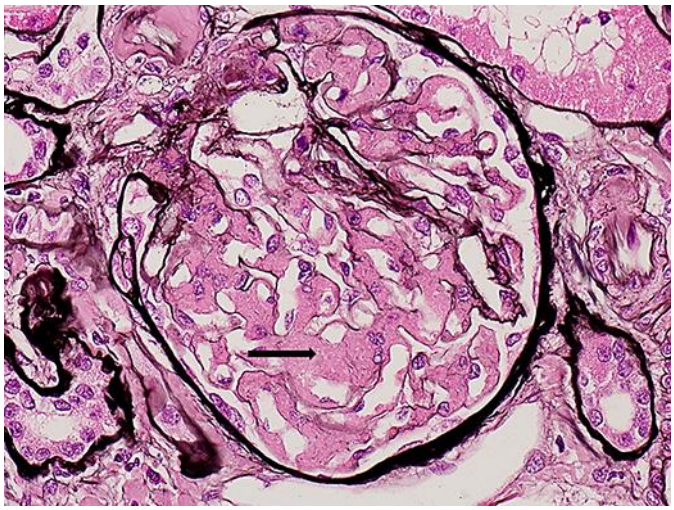

Fig. 1. Glomeruli show infiltration of mesangial areas and capillary loops by amorphous, pale eosinophilic material (arrow) characteristic of amyloid. Jones silver. ×40.

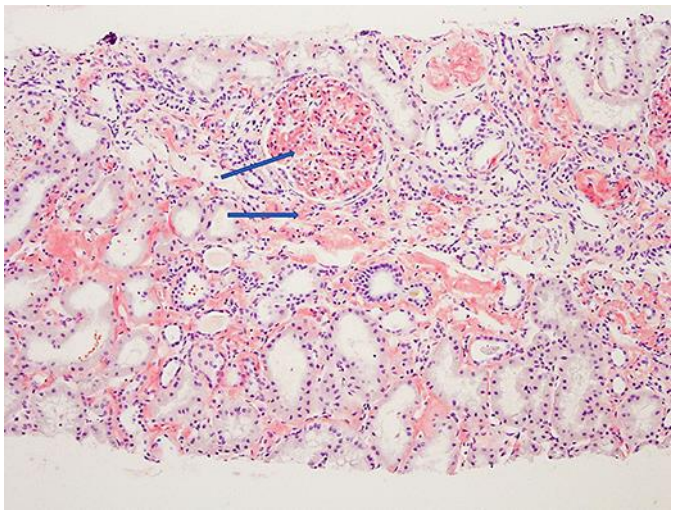

Fig. 2. The interstitium and glomeruli are diffusely infiltrated by congophilic amorphous material (arrows) consistent with amyloid. Congo red. ×10.

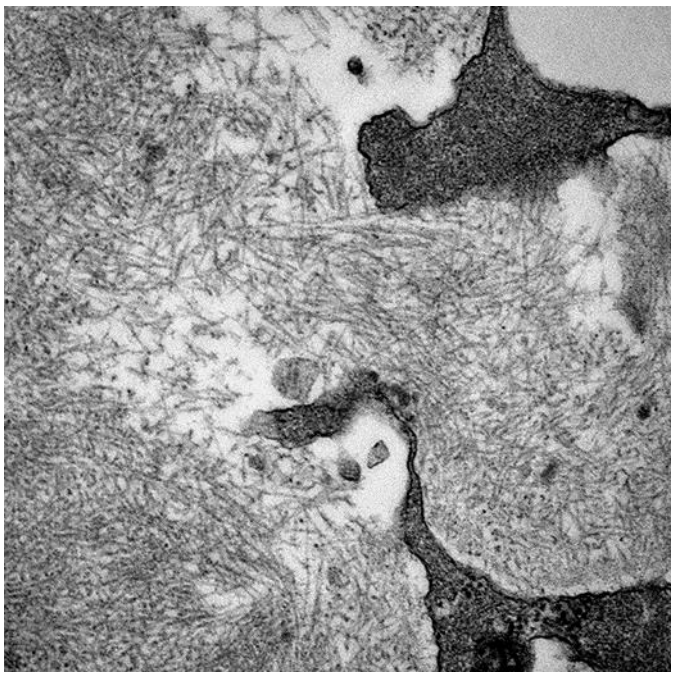

Fig. 3. Electron micrograph showing haphazardly arranged fibrils within the glomerulus characteristic of amyloid fibrils, averaging 9.8 nm in thickness.

Table 1. Laboratory test results at the time of initial evaluation

	Value	Reference range
Hemoglobin	11.3 g/dL	11.5–15.5 g/dL
White blood count	7.4×10^9/L	$3.4–10.4\times10^9$/L
Platelets	156×10^9/L	$150–425\times10^9$/L
Urea nitrogen	21 mg/dL	7–20 mg/dL
Creatinine	1.8 mg/dL	0.7–1.3 mg/dL
Estimated GFR	28 mL/min/m^2	
Calcium	8.8 mg/dL	8.6–10.6 mg/dL
Phosphorus	3.2 mg/dL	2.3–4.7 mg/dL
Alkaline phosphatase	111 U/L	125–243 IU/L
SGOT	34 IU/L	0–35 IU/L
SGPT	21 IU/L	0–40 IU/L
Albumin	3.8 g/dL	3.4–4.8 g/dL
Magnesium	1.8 mg/dL	1.6–2.6 mg/dL
Cholesterol	98 mg/dL	<199 mg/dL
HDL	42 mg/dL	>46 mg/dL
Triglycerides	144 mg/dL	<149 mg/dL
LDL cholesterol	111 mg/dL	<129 mg/dL
Urine microscopy	RBC 0–1/HPF, WBC 0–3/HPF, no dysmorphic RBCs, no casts	
Urine albumin/creatinine ratio	45 mg/g	
Urine protein/creatinine ratio	135 mg/g	

GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RBC, red blood cells; WBC, white blood cells; HPF, high-power field.

Table 2. Clinical features of patients diagnosed with ALECT2

	Larsen et al. [2] (New Mexico) (*N* = 18)	Larsen et al. [7] (Egypt) (*N* = 36)	Murphy et al. [9] (*N* = 10)	Larsen et al. [8] (*N* = 40)	Said et al. [10] (*N* = 72)
Age (mean), years	62.3	59.1	68	70.6	65.5
Racial distribution	Hispanic 16/18	N/R	Hispanic 7/10	Hispanic 35/40	Hispanic 66/72
Gender (M/F)	13/5	20/16	5/5	25/15	37/35
Glomerular involvement, %	28	84	90	88	91.7
Vascular involvement, %	44	76	90	83	84.3
Initial Cr, mg/dl	N/R	N/R	4.4	2.8	2.3
Stable renal function at follow-up, %	N/R	N/R	29.7	31.3	39.1
Progressive renal failure at follow-up, %	N/R	N/R	10	62	29
ESRD, *n* (%)	N/R	N/R	1 (10)	6[a] (27)	25[b] (39)
Mortality, %	N/R	N/R	10	N/R	6.3

N, total number of patients; M, male; F, female; Cr, creatinine; ESRD, end-stage renal disease; N/R, not reported. [a] Out of 22 patients. [b] Out of 64 patients.