LECT-2 amyloidosis: what do we know?

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ABSTRACT
Amyloidosis is a rare group of diseases characterized by abnormal folding of proteins and extracellular deposition of insoluble fibrils. It can be localized to one organ system or can have systemic involvement. The kidney is the most common organ to be involved in systemic amyloidosis often leading to renal failure and the nephrotic syndrome. The two most common types of renal amyloidosis are immunoglobulin light chain-derived amyloidosis (AL) and reactive amyloidosis (AA). A novel form of amyloidosis (ALECT2) derived from leukocyte chemotactic factor 2 (LECT-2) and primarily involving the kidneys was first described by Benson et al in 2008. The liver was subsequently identified as the second most common organ involved in ALECT2 amyloidosis. LECT-2 is a unique protein that can form amyloid deposits even in its unmutated form. Patients with ALECT2 present with minimal proteinuria in contrast to other forms of amyloidosis especially AL and AA. They may present with slightly elevated serum creatinine. Nephrotic syndrome and hematuria are rare. ALECT2 can be found in association with other types of amyloidosis as well as malignancies or autoimmune diseases. ALECT2 may be confused with amyloidosis associated with light and heavy chain monoclonal gammopathy if the immunofluorescence is positive with anti-light chain and anti-AA sera. The other organs involved are the duodenum, adrenal gland, spleen, prostate, gall bladder, pancreas, small bowel, parathyroid gland, heart, and pulmonary alveolar septa, but consistently uninvolved organs included brain and fibroadipose tissue. A renal biopsy along with characteristic features found on immunohistochemistry and mass spectrometry is diagnostic of ALECT2. ALECT2 should be suspected when all markers for AL and AA are negative. Proper diagnosis of ALECT2 can determine need for supportive care versus more aggressive interventions.

INTRODUCTION
Amyloidosis represents a group of diverse disorders characterized by abnormal folding of proteins and extracellular deposition of insoluble fibrils. There are over known 36 proteins which can form amyloid. The deposition of these abnormal amyloid fibrils in various tissues can ultimately lead to organ damage. Amyloidosis can manifest locally or systemically but can affect any organ. The most common organs involved in systemic amyloidosis include skin, heart, liver, renal, digestive tract, and nervous system. However, the kidney is probably the most commonly involved organ and when affected can result in nephrotic syndrome and renal failure. Historically, the two most common types of amyloid disorders leading to renal involvement are AL and AA. There are some hereditary forms of amyloidosis which are derived from fibrinogen A, apolipoprotein, gelsolin, and lysozyme affecting the kidney, but these are exceedingly rare. In 2008, Benson et al reported a case in which a patient presenting with nephrotic syndrome and renal failure leading to dialysis was found to have isolated deposition of amyloid in the glomerulus. There were no other organs other than kidney affected and immunohistochemistry (IHC) of the renal biopsies for known abnormal amyloid proteins was negative. Further biochemical analysis of the fibrils confirmed that they represented a novel renal amyloid protein which was identified as leukocyte chemotactic factor 2 (LECT-2). Amyloidosis restricted to the kidney is not common and this new renal predominant disorder was termed ALECT2. Subsequent reports demonstrated that among previously unidentified and unclassified renal-limited amyloidosis, ALECT2 was common. The deposition of LECT-2 was different from other types of renal amyloid in demonstrating conglobula within all compartments of the kidney including mesangium, glomerular basement membrane, interstitium, arterioles, and arteries. Although initially it was identified as renal-limited amyloidosis, recent reports demonstrate involvement of liver as well as subclinical involvement of the spleen, bowel, adrenal glands, lung, prostate, gallbladder, pancreas, and parathyroid gland. It appears to spare nerves and fat but renal manifestations predominate. The molecular basis and pathogenesis are unclear and not well defined but ALECT2 has a better prognosis than AL or AA. The initial reports of ALECT2 suggested that it preferentially affects patients with Hispanic ethnicity particularly Mexicans and Mexican-Americans in southwestern part of the USA. However, subsequent reports documented the disease in Punjabis, First Nations peoples in British Columbia, Egyptians, Chinese of Han ethnicity, and Native Americans as well. The limitation of ALECT2 in non-Caucasian populations remains unclear.
Pathophysiology

LECT-2 was first identified in 1996 by Yamagoe et al and recognized as a chemotactic factor for neutrophils.⁴ Lu et al subsequently demonstrated that treatment with LECT-2 improved protective immunity via enhancement of macrophage functions in septic mice.⁵ It is now clear that it is a versatile protein involved in chemotaxis, cell proliferation, inflammation, immunomodulation and carcinogenesis.⁶ The protein consists of 133 amino acids, three intramolecular disulfide bonds which bind a single Zn molecule and its gene located in chromosome 5q31.1-q32.⁷ This chromosome harbors a cluster of genes involved in immune-regulatory cytokines.

Among patients with ALECT2, there are several polymorphisms⁸–¹⁴ and few mutations⁵ ¹⁵ ¹⁶ that have been identified. A polymorphism of the G nucleotide at position 172 of the LECT-2 gene has been noted, especially in patients from Latin America, which is associated with renal amyloidosis but the polymorphism is insufficient for disease progression and an identified second hit is suspected.¹⁵ Another single nucleotide polymorphism in the LECT-2 gene is Val38Ile which is frequently seen in renal ALECT2.¹⁷ A recent report suggests that removal of LECT-2’s single-bound Zn appears to be necessary for fibril formation.¹⁸ Thus, it is postulated that removal of zinc together with an associated mutation leads to abnormal LECT-2 and results in ALECT2.

The LECT-2 protein is produced in the liver and hepatocytes show diffuse immune staining of LECT-2 within their cytoplasm.¹⁹–²¹ LECT-2 is a hepatokine which gets increased in response of deposition of fat inside liver. Elevated LECT-2 mRNA levels have been found in obese patients with hepatic steatosis.²² Aggregation of abnormal circulating LECT-2 protein results in amyloidosis. The exact pathophysiology is unclear, but it is possible that a combination of genetic factors or mutations in conjunction with environmental factors (obesity) results in upregulation of LECT-2 production among hepatocytes. The elevated unstable/misfolded LECT-2 protein in combination/interaction with other circulating factors such as components of the extracellular matrix ultimately leads to abnormal fibril production. These abnormal LECT-2 fibrils get deposited in interstitium of kidney and liver and impede their physiologic functions.²³ There is an association between LECT-2 and pathophysiology of diseases among variety of different organ systems including renal, gastrointestinal, hepatic, skeletal, immune system, endocrine and metabolic, oncology, pulmonary, and vascular.²⁴

Clinical manifestations of renal ALECT2 amyloidosis

The hallmark of other non-ALECT2 amyloid disease such as AL or amyloidosis of transthyretin (ATTR) is the multi-organ involvement, which raises the suspicion of a systemic illness. In these types of amyloidosis, there is frequent cardiac, nervous, renal, dermatological, and other organ system involvement. Among such amyloidosis entities, the need for a kidney biopsy is less.²³ The diagnosis of amyloid deposition in AL or ATTR can be made via skin, bone marrow or cardiac biopsy or non-invasive tests such as serum protein electrophoresis or bone scan that play an important role in diagnosis. Once amyloid is identified, then it can be further classified via liquid chromatography/mass spectrometry (LC/MS).

However, in ALECT2, there is very minimal cardiac, nervous system, skin, or other organ involvement, but renal and to a lesser degree hepatic pathology is the likely presenting clinical feature. In fact, ALECT2 was first identified in 2008 in a patient with chronic kidney disease (CKD) secondary to nephrotic syndrome with no other clinical organ involvement.⁴ Later, many cases describing the hepatic involvement were also reported and some autopsy studies documented ALECT2 deposition in other organs. Nevertheless, renal pathology remains the most common clinical presentation as the sole clinical feature. In the USA, there is a strong ethnic bias for renal ALECT2 in contradistinction to other systemic amyloidosis with 88%–92% of cases reported among Hispanics, specifically Mexican-Americans.²³ The typical presentation in the USA is an elderly Hispanic patient presenting with chronic renal insufficiency with or without proteinuria. It is not unique to this ethnic group as ALECT2 has been described in Punjabis, First Nations people in British Columbia, Arabs, Israelis, and Native Americans.²¹

Three large series of ALECT2-documented patients totaling 144 cases, have been previously reported that provided the summary highlighting and elucidating the renal manifestations.²⁵–²⁷ The median age at diagnosis is 69 years old, with only 5 patients less than 50 years of age at diagnosis. Men and women are equally affected and there is minimal presence of family history of amyloidosis. Patients typically present with isolated CKD with a mean serum creatinine at diagnosis ranging from 2.8 to 3 mg/dL. The serum creatinine at time of diagnosis is not necessarily proportional to total renal amyloid load or with degree of amyloid in glomeruli, interstitium or vessels but may correspond to the percentage of global glomerulosclerosis, tubular atrophy/interstitial fibrosis and arteriosclerosis.¹⁰

An interesting feature of renal ALECT2 is that proteinuria is minimal in comparison with other forms of amyloidosis especially AL or ATTR. Nephrotic range proteinuria was noted in only 33% of 72 patients in the series by Said et al and lacking altogether in 21%,¹⁰ in the series by Larsen et al, proteinuria was noted in 33% and nephrotic range proteinuria in only 23%.⁹ The bland urinary sediment may reflect early glomerular involvement by amyloid that reflects more characteristic feature of renal ALECT2.²⁴ When nephrotic range proteinuria is present in ALECT2, it is important to consider that it may be due to a concomitant underlying nephropathy like diabetic glomerulosclerosis or IgA nephropathy.¹⁰ It may have concurrent membranous glomerulopathy, acute tubular injury, interstitial nephritis, or arterionephrosclerosis, or podocytopathy/nephrotic syndrome.²⁵ ²⁶ Microhematuria is uncommon. The most common associated comorbidities are chronic hypertension and diabetes. The worsening of renal failure to endstage renal disease ranges from approximately 30% to 40% cases.⁹ ¹⁰ ALECT2 can be found in association with other types of amyloidosis like immunoglobulin λ light chain amyloidosis,²⁷ plasma cell dyscrasia,¹⁰ or membranous nephropathy,²⁸ some type of carcinoma (kidney, bladder, prostate, uterine and breast) or history of autoimmune disease.¹⁰

A kidney biopsy conducted to investigate the cause of abnormal kidney function demonstrating amyloid deposition is the first clue for consideration of ALECT2. IHC can be conducted with commercially available antibodies. ALECT2 kidney deposition is strongly congoophilic showing apple-green birefringence under polarized light. Along with Congo red-positive amyloid deposits, there are some other notable distinguishing pathologic characteristics. Renal ALECT2 demonstrates preferential diffuse cortical interstitial involvement in contrast to other amyloid disorders which affect the medullary interstitium. In contrast to AL and AA with prominent glomeruli and vessel amyloid deposition, the glomerular and vascular amyloid deposits in ALECT2 may be absent or may range from mild to marked staining. Immunofluorescence analysis, which is part of routine work-up for amyloidosis, is frequently negative in ALECT2 although false-positive staining for IgG may occur on rare occasions. Therefore, LC/MS proteomics along with IHC-based approach becomes extremely helpful for identification of ALECT2 and differentiating it from other forms of amyloidosis. LC/MS remains the most sensitive and specific method to diagnose ALECT2 and other forms of amyloidosis to date. There is a possibility of missing ALECT2 as contributing to the renal pathology due to the confounding comorbidities seen in these patients. Thus, nephrologists and pathologists should have a higher degree of suspicion for ALECT2. This is especially true in older individuals of Mexican origin or the other reported ethnicities who present with CKD with absent or mild proteinuria. A Congo red stain should be performed and congoophilic differences between ALECT2 and other amyloidosis subtypes should be appreciated. If ALECT2 is the predominant pathology, there is no known current treatment and early detection of ALECT2 may avoid initiation of unnecessary or potentially harmful therapies. Additional research on the natural history and potential therapies of ALECT2 disease is needed. The pioneer cases or case series of ALECT2 reported over the last decade has been enlisted in Table 1.

Hepatic ALECT2 amyloidosis

Interestingly, the identification of ALECT2 and its role in renal pathology has led to the observation of LECT-2 playing a role in liver health, disease, and regeneration as well. As mentioned previously, synthesis of LECT-2 protein from hepatocytes is regulated by β-catenin and acts as a versatile chemokine. In an elegant study, Takata et al proposed a schema of the effects of LECT-2 on liver inflammation. They demonstrated elevated LECT-2 protein levels are found in response to high fat intake and trigger lipopolysaccharide-stimulated C-Jun N-terminal kinase phosphorylation which macrophage-mediated inflammation of liver tissue. This transforms minor hepatic steatosis to non-alcoholic steatohepatitis. These findings suggest that treatment targeting the LECT-2 protein could help in disintegrating hepatic steatosis from inflammation. The liver is also a commonly involved organ by ALECT2 and compromises between 60% and 90% of cases of systemic amyloidosis. Mereuta et al described and evaluated 130 cases of unclassified hepatic amyloidosis that were identified histologically. Using LC/MS technique, AL was confirmed to be the most frequent etiology of amyloidosis while ALECT2 accounted for 25% of cases. Prior to this report, ALECT2 was not a known cause of hepatic amyloidosis. Like the original renal ALECT2 reports, this series from the USA also showed ethnic predominance among Hispanics in the hepatic ALECT2 cases. The pathologic characteristics of hepatic ALECT2 are different and unique from those of AL. In Mereuta et al’s study, all the hepatic ALECT2 specimens demonstrated globular amyloid deposits localized along the perportal parenchyma or at the periphery of the portal triad and around central venules. These characteristic features of globular pattern of ALECT2 deposits contrast with hepatic AL which leads to perisinusoidal amyloid deposition.

The clinical significance of making the correct diagnosis of hepatic ALECT2 is important to prevent misdiagnosis as AL, AA, or ATTR amyloidosis which have different therapeutic options and clinical course. Hepatic ALECT2 has no therapeutic options available but the clinical course may be more indolent like renal ALECT2. However, there are reports of hepatic ALECT2 leading to cirrhosis, portal hypertension and esophageal bleeding suggesting that hepatic ALECT2 may be an under-reported entity. Since LECT-2 is synthesized in the liver, it has been noted that LECT-2 levels decrease in liver failure and increase when liver function recovers. Thus, the serum LECT-2 levels may serve as a prognostic indicator in acute liver failure and LECT-2 may participate in liver regeneration, but further studies are needed. Okabe et al have evaluated the role of LECT-2 as a potential biomarker in hepatocellular carcinoma (HCC). LECT-2 levels were found to be elevated in HCC as compared with patients with cirrhosis or healthy controls. There is one report of intrahepatic cholangiocarcinoma with concomitant ALECT2.

Other organ system involvement

It is very likely that ALECT2 is a systemic amyloid disease however renal manifestations dominate the clinical picture. Liver is commonly involved and few reports link with abnormal liver pathology. Most of the other organ involvement is subclinical in nature. A study from the Mayo Clinic including 120 patients with ALECT2 diagnosed by LC/MS found that 72 patients had kidney, 36 liver, 5 spleen, 3 prostate, and 1 each of gallbladder, pancreas, small bowel, and parathyroid gland involvement. In most ALECT2 cases reported in the past, kidney biopsy was performed and early detection of ALECT2 may avoid initiation of unnecessary or potentially harmful therapies. In the series of hepatic ALECT2 reported by Mereuta et al, none of the patients had clinical extrahepatic organ involvement. In the series of hepatic ALECT2 reported by Mereuta et al, none of the patients had clinical extrahepatic organ involvement. An autopsy series from New Mexico found that ALECT2 is common among Hispanics in New Mexico and likely represents an underdiagnosed etiology of CKD in this population. In this series, amyloid deposits were observed in a consistent pattern primarily involving the kidneys, liver, spleen, adrenal glands, and lungs. None had deposition in the cardiac myocardium, brain, skin, or fibroadipose tissue. Only one case has been reported in the literature describing cardiac ALECT2 and another reported a rare presentation of pulmonary-renal syndrome. It is conceivable that other
Table 1  The pioneer cases or case series published on ALECT2 amyloidosis are enlisted with description of findings of histopathology, immunochemistry, immunofluorescence and tandem mass spectrometry.

| Authors       | Number of ALECT2 cases | Prevalence of ALECT2 among amyloidosis cases | Gender | Age (years) | Race | Family history | History of cancer | Clinical presentation | Monoclonal gammopathy/positive staining with anti-light chain serum or anti-AA | Immunohistochemistry/immunofluorescence with anti-ALECT2 antibody | LC/MS performed and reported | Mutations reported on DNA analysis | Polymorphism on DNA analysis | Follow-up |
|---------------|------------------------|---------------------------------------------|--------|-------------|-----|----------------|-------------------|----------------------|-------------------------------------------------|---------------------------------------------|-----------------------------|-----------------------------|---------------------------------|--------------|------------|
| Benson et al  | 1 renal                | NA                                         | F      | 60s         | N/A | N/A            | + renal           | nephrotic syndrome   | N/A                                             | + in 1                                      | N/A                         | +                           | N/A                             | 2 years       |
| Larsen et al  | 7 renal                | NA                                         | N/A    | N/A         | NA  | N/A            | N/A               | nephrotic syndrome   | N/A                                             | N/A                         | +                           | +                           | N/A                             |               |
| Murphy et al  | 10 renal               | Third most common                          | N/A    | 58–84       | 7 Mexican-Americans | N/A            | nephrotic syndrome   | OAD with minimal proteinuria | N/A                                             | +                             | +                           | +                           | N/A                             | 7 followed, 1 ESRD, 1 death |
| Said et al    | 13 renal               | Third most common                          | 9 M/4 F| Median 68   | N/A | N/A            | 12 OAD, 2 nephrotic syndrome | N/A                                             | + in 1                                      | N/A                         | +                           | N/A                             |               |
| Larsen et al  | 40 renal               | Second most common                         | 25 M/15 F| Mean 70.6   | Mostly Hispanic | 2 brothers | N/A            | nephrotic syndrome   | OAD in 60% with 40% no proteinuria; most patients with nephrotic range proteinuria had a second glomerulopathy | N/A                             | +                           | N/A                             | +                           | 10% stable renal function; 62% progressive renal failure; 29% ESRD |
| Said et al    | 32 renal, 19 had another organ involvement| N/A                                         | 37 M/25 F | Median 65.5 | Mostly Hispanic | N/A            | N/A            | nephrotic syndrome   | OAD with variable proteinuria | +                             | N/A                         | +                           | +                           | 38.1% ESRD after 26 months; 28.7% had stable kidney function |
| Prasad et al  | 50 renal               | NA                                         | N/A    | N/A         | N/A | N/A            | N/A               | nephrotic syndrome   | N/A                                             | +                             | +                           | +                           | N/A                             |               |
| Mereuta et al | 32 hepatic             | Second most common                         | 12 M/20 F| Median 60.5 | Mostly Hispanic | N/A            | + Hepatosplenic     | Incidental chorioretinopathy, elevated transaminases | N/A                                             | +                             | -                           | +                             | N/A                             |               |
| Chandan et al | 27 hepatic             | N/A                                         | N/A    | Median age of 59 | N/A | N/A            | N/A               | nephrotic syndrome   | N/A                                             | +                           | +                           | +                           | N/A                             |               |
| Larsen et al  | 36 renal               | Second most common                         | 16 F/20 M| Mean age 59.1; youngest 30 | Egyptian | N/A            | nephrotic syndrome   | OAD                  | N/A                                             | +                           | N/A                         | +                           | N/A                             |               |
| Larsen et al  | 18 renal (autopsy series) | N/A                                         | N/A    | N/A         | Mostly Hispanic from New Mexico | N/A            | N/A            | nephrotic syndrome   | OAD                  | +                           | N/A                         | +                           | N/A                             |               |
| Rezvani et al | 24 renal, 11 hepatic   | N/A                                         | N/A    | Median 62   | Pakistani, Punjabi, Egyptian, Indian, Sudanese, Mexican | N/A            | N/A            | nephrotic syndrome   | OAD                  | +                           | N/A                         | +                           | N/A                             |               |

CKD, chronic kidney disease; ESRD, end-stage renal disease; F, female; LC/MS, liquid chromatography-mass spectrometry; LECT2, leukocyte chemotactic factor 2; M, male; N/A, not applicable.

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clinically significant organ involvement aside from renal or hepatic is under-recognized. Given the sparsity of skin or fat involvement, it is highly unlikely that less invasive procedures like biopsy of the skin or fat pad will be useful in documenting systemic ALECT2.

Diagnosis and treatment
Non-ALECT2 amyloid disorders frequently have cardiac, nervous system, fat or skin involvement in addition to renal dysfunction. In a patient where renal dysfunction or liver appears to be the sole clinical manifestation of amyloidosis, ALECT2 should be strongly considered. The typical presentation in the USA is an elderly Hispanic patient presenting with CKD with or without proteinuria in whom a concomitant diagnosis of diabetes or hypertension is not suspected to be a major contributing cause of the renal dysfunction. A renal biopsy should be conducted for evaluation of amyloid when indicated. ALECT2 should be suspected when markers for the other systemic amyloid disorders (AA, AL, and ATTR) are negative. Circulating LECT-2 levels are not useful in screening. There is one report describing the use of florbetapir radiotracer-based positron emission tomography/computed tomography (PET/CT) demonstrating remarkable uptake in the kidney in a patient with biopsy-confirmed ALECT2. Unlike AL or ATTR amyloid, there was no uptake to the heart but extremely active uptake to the involved ALECT2 kidney was noted. However, further studies are needed to make it more clear that florbetapir PET/CT can be used as a screening test.

On histopathology, ALECT2 is strikingly congophilic, demonstrates preferential diffuse cortical interstitial involvement, less medullary involvement, with variable glomerular and vascular amyloid deposition. This differentiates ALECT2 from other forms of amyloidosis with characteristic morphologic patterns such as predominant medullary involvement in apolipoprotein A-IV associated amyloidosis and predominant glomerular deposition in hereditary fibrinogen amyloidosis. Patients with ALECT2 with concomitant nephrotic syndrome must alert for possibility of concurrent podocytopathy and electron microscopy must be performed, especially if clinical findings are inconsistent with the affected kidney compartment.

The liver ALECT2 deposition, like the renal ALECT2, has a characteristic histologic pathology. ALECT2 liver deposits are noted to preferentially surround the central veins and along the periphery of the portal tracts with a very distinctive globular appearance. This contrasts with AL deposits which frequently exhibit a perisinusoidal distribution pattern. LC/MS proteomics is an excellent tool to subtype amyloidosis. It remains the most sensitive and specific method to differentiate ALECT2 from other forms of amyloidosis to date.

A critical need for accurate diagnosis, identification, and differentiation of ALECT2 from other systemic amyloidosis is to prevent unnecessary and potential harmful treatments. For example, if ALECT2 is misdiagnosed as amyloidosis caused by a subtle plasma cell dyscrasia, it may result in administration of chemotherapy. Unfortunately, at present, there is no specific treatment for ALECT2 in contrast to ATTR and AL amyloid. The treatment of ALECT2 is mainly supportive in nature and although the natural history is not well defined, it appears to be more indolent in course than AL or ATTR. A few reports have demonstrated donor-derived ALECT2 deposits in transplanted allografts which did not resolve over time but remained stable with no interference of allograft function. In instances where ALECT2 coexists with clinically significant IgA nephropathy and nephrotic syndrome, there is a benefit of treating with chemotherapy and/or steroids which are effective for the IgA nephropathy.

Summary
Since its original description 13 years back, we now know that ALECT2 is a common amyloid entity. It has an ethnic predisposition with predominantly interstitial renal distribution, usually misdiagnosed due to absence of monoclonal gammopathy, absence of family history of amyloidosis, rarity of extrarenal involvement and relative absence of marked proteinuria. It is still likely to be unrecognized and underappreciated. We hope that an additional research on the natural history and potential therapy for ALECT2 will be forthcoming in the future.

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Review


