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ORIGINAL ARTICLE

Prevalence and organ distribution of leukocyte chemotactic factor 2 amyloidosis (ALECT2) among decedents in New Mexico

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Abstract

Leukocyte chemotactic factor 2 (LECT2) amyloidosis is one of the most recently described types of amyloidosis. Since its description, it has been found to be one the most common types of amyloidosis in large series of amyloid cases involving the kidney and liver in the United States, where it primarily affects patients of Hispanic ethnicity. We sought to investigate the prevalence of this disease among Hispanic adult decedents who had an autopsy performed at the New Mexico Office of the Medical Investigator and determine the organ distribution of amyloid deposition. LECT2 amyloid deposits were identified within the kidney in 3.1% of Hispanic decedents. It was consistently deposited in the liver, spleen, adrenals, and lungs but did not involve the myocardium or brain. LECT2 amyloidosis is likely not rare among Hispanics in the Southwest United States and could represent an important but under-recognized etiology of chronic kidney disease in this population.

Abbreviations: LECT2, leukocyte chemotactic factor 2; ALECT2, leukocyte chemotactic factor 2-type amyloidosis

Keywords

Amyloidosis, autopsy, chronic kidney disease, Hispanic, leukocyte chemotactic factor 2, LECT2, renal biopsy

History

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Introduction

Amyloidosis is the abnormal deposition and accumulation of insoluble protein fibrils in the parenchyma of tissues leading to organ failure. These protein deposits form a characteristic beta-pleated sheet conformation which leads to the diagnostic morphologic finding of Congo red positive staining with green birefringence upon polarization. The kidney is the most common organ involved in systemic amyloidosis, commonly leading to renal failure and nephrotic syndrome [1]. There are now >30 proteins known to form amyloidosis in humans [2]. Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is one of the most recently described forms [3] and typically presents with slowly progressive renal failure [4].

Several surprising findings have come to light since the identification of ALECT2. Perhaps the most surprising is that, despite being the last of the known amyloid proteins described, it is actually quite prevalent. Two large case series focusing on renal amyloidosis have identified ALECT2 as the second or third most common form of amyloidosis diagnosed in the kidney [5,6]. Additionally, a recent large case series in the liver identified it as the second most common form of hepatic amyloidosis [7]. Another interesting finding is that the vast majority of patients suffering from this disease are of Hispanic ethnicity [8]. The disease has been shown to be particularly common in the Southwest United States where, in one study, 21 of 40 amyloid cases (54%) were typed as ALECT2 [4]. Currently, there are no known biomarkers for this disease and the only way to diagnose it is by kidney biopsy. Therefore, the prevalence of ALECT2 is unknown and it is likely an underdiagnosed etiology of renal failure in the Southwest US due to the fact that chronic kidney disease is not typically an indication for renal biopsy.

We sought to determine the prevalence of ALECT2 among adults in the Southwest United States. Since a non-invasive diagnostic method to screen for the disease does not exist, we pursued this question through analyzing the kidneys and other tissues from autopsies performed in New Mexico. No ALECT2 autopsy studies have been previously undertaken. However, one of the few amyloidosis autopsy case series present in the literature had an interesting conclusion that might be relevant to ALECT2 [9]. Buck et al. published in 1989 a description of 467 autopsies with amyloidosis at the Los Angeles County Medical Center. They found a statistically significant increase in amyloidosis among patients with Hispanic last names compared with Caucasians. The overall rate of amyloidosis in Hispanic adults was 4.25% compared

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with 0.7% in other adult ethnicities combined. They specifically noted that there was an increase in amyloid that was not AL or AA in these Hispanic patients. ALECT2 was not described at that time but it leads one to suspect that this is what they were detecting. We present the results of our case series investigating the presence of ALECT2 among decedents in New Mexico.

Methods

The database from New Mexico Office of the Medical Investigator was searched between 2010 and 2012 for decedents over the age of 45 at the time of death. Demographic information including age at death, race, and gender of each decedent to be studied was included in the database. These cases were studied for the prevalence of ALECT2. This study was done in two phases, an initial analysis which comprised consecutive autopsies from decedents over the age of 45 at the time of death that included all ethnicities followed by a more focused analysis which comprised consecutive autopsies from decedents over the age of 45 at the time of death that included only the ethnicities in New Mexico which have formerly been described to be most affected by this disease, namely, Hispanics and Native Americans. Specifically, the initial analysis comprised 524 consecutive cases from the database including decedents from all ethnicities and the focused analysis examined 477 consecutive cases in the database from decedents of Hispanic and Native American ethnicity. The study protocol was approved by the New Mexico Office of the Medical Investigator. All information was de-identified and the protocol used only tissue routinely collected at autopsy.

The paraffin block(s) which contained kidney tissue from each case was pulled and shipped to Nephropath in a de-identified manner. At Nephropath, one section was cut at a thickness of 5 μm from each block for Congo red staining. No further testing was performed on Congo red negative cases. Cases which showed deposition of Congo red-positive material were then polarized to determine whether the material showed the characteristic green birefringence of amyloidosis. A panel of antibodies was used to type the amyloid deposits, when detected. This panel included immunoperoxidase stains for AA (Dako, Carpenteria, CA) and LECT2 (R&D Systems, Inc., Minneapolis, MN) as well as paraffin immunofluorescence for kappa and lambda (both from Dako, Carpenteria, CA) [10]. These stains were scored as positive or negative and diagnosed as the type of amyloidosis corresponding to the positive stain. Cases were listed as ''undetermined'' type of amyloidosis if all stains were negative. There were no cases in which more than one stain was positive. No further studies were performed on non-LECT2 cases. Once confirmed for ALECT2, all of the remaining tissue paraffin blocks were shipped to Nephropath. A 5-μm-thick section was cut from each of these blocks and stained for Congo red so that the organ distribution of the amyloidosis could be determined.

Results

The initial phase, which included all ethnicities, was composed of 524 cases of the following ethnicities: 318 Caucasians, 144 Hispanics, 41 Native American Indian, 15 African Americans, two Asians, and four unknown. There were a total of four cases of renal ALECT2 in this cohort (0.7%), including 3/144 Hispanics (2.1%) and 1/318 Caucasians (0.3%). No ALECT2 was identified in other ethnicities in this phase.

The second phase of investigation enriched the cohort for the populations of interest with regard to ALECT2. In this phase, a total of 477 cases were studied, including 376 Hispanics and 101 Native American Indians. Combining both phases, there were 16 cases of ALECT2 identified among 520 Hispanics (3.1%). One case of ALECT2 was identified among a total of 142 Native American Indians (0.7%). A total of six non-LECT2 amyloidosis cases were identified (three in the first phase and three in the second phase). These included two cases of AL lambda among non-Hispanic Caucasians and four cases of unknown amyloid type among Hispanics. Overall, ALECT2 was four times more prevalent among Hispanic adults than all other types of renal amyloid combined. The mean age of ALECT2 patients was 62.3 years (range 47–98). There were 13 males and five females with ALECT2. The combined analysis showing amyloid prevalence in all ethnicities is detailed in Table 1.

The pathologic distribution of ALECT2 is shown in Table 2 and Figure 1. The amyloid deposits were present in the renal cortical interstitium in all cases. There was frequent involvement of the portal tract of the liver, spleen, pulmonary alveolar septa, and adrenal gland. Consistently uninvolved organs included brain, myocardium, fibroadipose tissue (both subcutaneous and perinephric), and pancreas. Arterial walls were involved by amyloid in many organs including kidney, heart, liver, spleen, lung, and bowel. The brain regions sampled included the hippocampus and entorhinal cortex in nine cases,

Table 1. Amyloid subtypes by ethnicity.

Ethnicity (#)	Total amyloid cases (%)	ALECT2 cases (%)	AL cases (%)	AA cases (%)	Other amyloid cases (%)
Hispanic (520)	20 (3.8)	16 (3.1)	0	0	4 (0.7)
Caucasian, not Hispanic (318)	3 (0.9)	1 (0.3)	2 (0.6)	0	0
Native American Indian (142)	1 (0.7)	1 (0.7)	0	0	0
African American (15)	0	0	0	0	0
Other (6)	0	0	0	0	0

ALECT2, leukocyte chemotactic factor 2 amyloidosis; AL, amyloid light-chain; AA, Amyloid A amyloidosis.

Table 2. Organ involvement by ALECT2 deposits.

Location of deposits	Proportion of cases with involvement (%)
Kidney	18/18 (100%)
-Glomerular	5/18 (28%)
-Arteries	8/18 (44%)
-Cortex interstitium	18/18 (100%)
-Medulla interstitium	2/18 (11%)
-Perinephric fat	0/10
Liver	16/17 (94%)
-Portal tract	16/17 (94%)
-Lobule	5/17 (29%)
-Arteries	11/17 (65%)
Spleen	7/7 (100%)
-Arteries	4/7 (57%)
-Red pulp	7/7 (100%)
-Periarterial lymphatic sheath	0/7
Lung	17/18 (94%)
-Alveolar septa	17/18 (94%)
-Arteries	1/18 (6%)
-Bronchioles	0/18
Pancreas	0/4
Adrenal gland	5/5 (100%)
-Cortex	5/5 (100%)
-Medulla	5/5 (100%)
Heart	5/17 (29%)
-Myocardium	0/17
-Arteries	4/17 (24%)
-Pericardium	1/17 (6%)
Brain	0/12
Thyroid	0/3
Trachea	0/2
Bladder	0/3
Bone marrow	0/1
Uterus	0/1
Ovary	0/1
Prostate	0/2
Stomach	0/2
Colon	1/2 (50%)
-Mucosa/submucosa	0/2
-Arteries	1/2 (50%)
Small bowel	0/2
Appendix	0/1
Tongue	0/1
Lymph node	0/1
Skin	0/3
Subcutaneous fibroadipose tissue	0/3

deep gray matter in two cases, cerebellum with dentate nucleus in two cases, medulla and cervical cord in one case, pons in one case, midbrain in one case, and cingulate gyrus and corpus callosum in one case.

Discussion

LECT2 amyloidosis is the most recently described renal amyloidosis and our understanding of this disease continues to evolve. Perhaps the most surprising aspect of this disease is how common it is in certain ethnicities. We suspect that it is an underdiagnosed etiology of renal failure in elderly patients of Mexican descent due to the fact that there is no way to detect its presence other than renal biopsy, and slowly progressive renal failure with bland urine sediment is not a common biopsy indication.

In our series, ALECT2 had a prevalence of 3.1% among Hispanics. There was also one case detected out of 318 (0.3%) in a non-Hispanic Caucasian and one case out of 142 (0.7%) in a Native American Indian. This prevalence of ALECT2 among Hispanic adults in New Mexico is similar to the degree of amyloidosis seen in a previous autopsy study from Los Angeles, CA [9]. This study showed that, among 40 832 adult autopsies, significantly more amyloidosis was found in decedents of Hispanic ethnicity. Specifically, 4.25% of Hispanic decedents showed evidence of amyloid deposition compared with 0.7% of all other ethnicities. ALECT2 was not described at the time of this previous case series but, based on the results of the current study, a significant proportion of the amyloid seen in Hispanics in this series likely represented ALECT2.

Case reports and small case series have detailed identification of ALECT2 in a variety of organs but this disease appears to most commonly come to clinical attention by causing progressive renal failure [4,11]. Reports of other organs affected by deposition of LECT2 amyloid include lung, adrenal, prostate, gallbladder, pancreas, small bowel, and parathyroid gland [11–13]. Deposition outside the kidney can result in clinically apparent disease. However, in many organs such as the liver, it is an incidental discovery when the organ is sampled for other unrelated disorders [7]. Our autopsy series showed that the distribution of organ involvement and the pattern of deposition within the individual organs were fairly consistent. For example, renal, lung, and hepatic involvement were uniformly present. Within the kidneys, deposition was predominantly within the interstitium of the cortex, which is typical for ALECT2, while a specific globular pattern of deposition is characteristically present in the liver [14]. ALECT2 does not deposit in the myocardium and it is, therefore, unlikely to result in a restrictive cardiomyopathy.

The current autopsy series is small compared with the population of Hispanics in the Southwest US. Therefore, we cannot know with certainty if it is representative of the burden of ALECT2 in this population. Autopsies are only performed at the Office of Medical Investigation in approximately one-third of the cases it receives and patients who are closely followed for a known medical condition are less likely to undergo autopsy than those with an unknown medical history. Therefore, we would speculate that this study is more likely to underrepresent the burden of disease in the Southwest since the decedent population we targeted is enriched for patients without a known medical cause of death.

Conclusion

We demonstrate in this autopsy series that ALECT2 amyloidosis is not a rare disease among Hispanics in New Mexico and likely represents an underdiagnosed etiology of chronic kidney disease in this population. The amyloid deposits in a consistent pattern primarily involving the kidneys, liver, spleen, adrenals, and lungs. Importantly, no deposition was identified in the cardiac myocardium or brain. The lack of deposition in the skin or fibroadipose tissue is also important as it makes the possibility of a less invasive diagnostic procedure such as fat pad aspirate or skin biopsy unlikely to

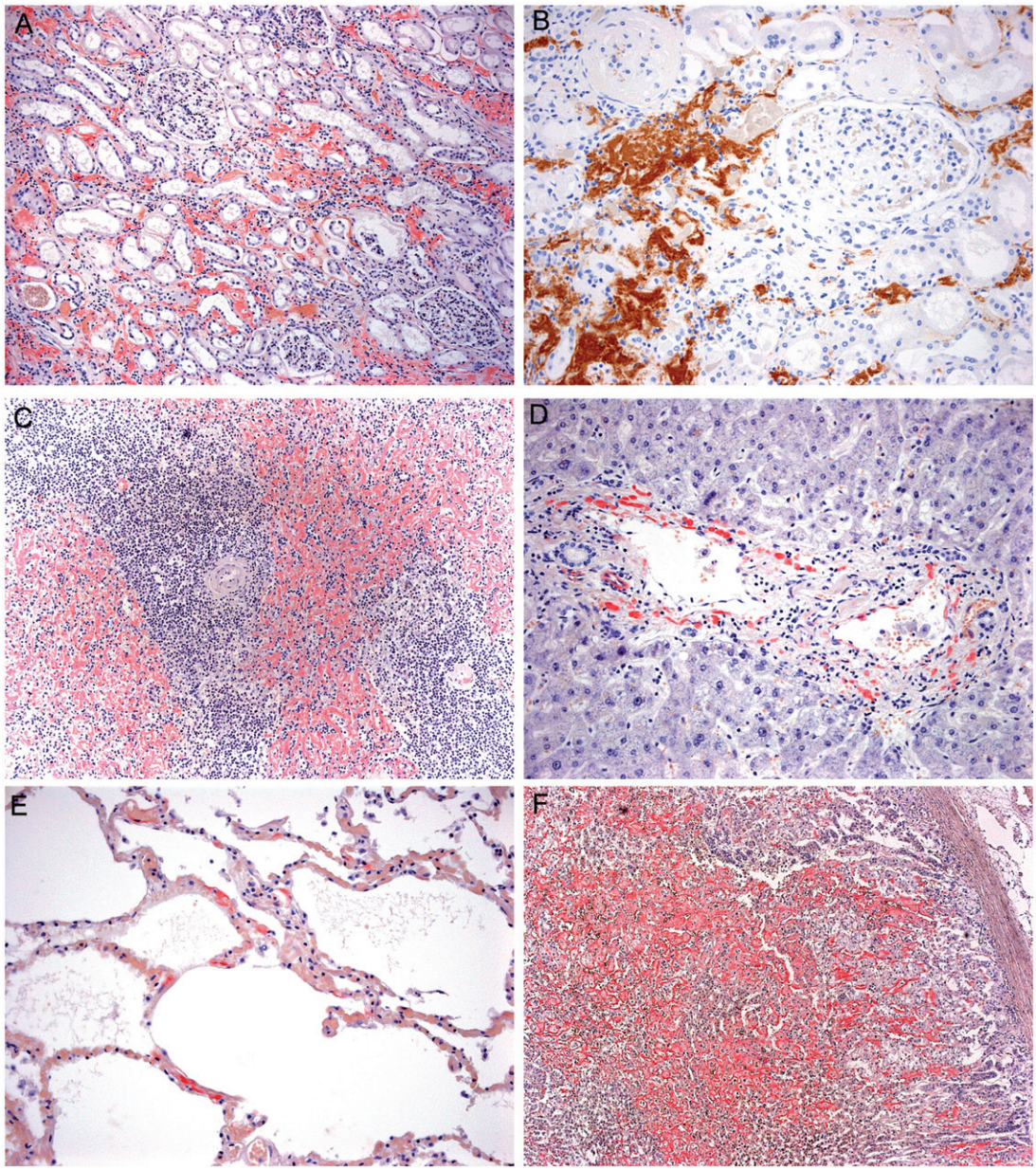

Figure 1. Leukocyte chemotactic factor 2 amyloidosis. (A) Uptake of Congo red by amyloid deposits in the renal cortex (original magnification ×100). (B) Reactivity of interstitial amyloid deposits with an anti-LECT2 antibody (immunoperoxidase technique, ×200). (C) Extensive amyloid deposition within the red pulp of the spleen (Congo red stain, original magnification ×100). (D) Globular pattern of amyloid deposition within the portal tract of the liver (Congo red stain, original magnification ×200). (E) Amyloid deposition in the pulmonary septa (Congo red stain, original magnification ×400). (F) Dense amyloid deposition in the cortex and medulla of the adrenal gland (Congo red stain, original magnification ×100).

be useful. Future studies investigating non-invasive biomarkers of disease are needed to advance our understanding of this disease and facilitate development of therapeutics.

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Declaration of interest

The authors report that they have no conflicts of interest. This study was supported by a research grant from Alnylam Pharmaceuticals, Cambridge, MA.

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