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ALECT2 Amyloidosis Review

Bushra Firdous Shaik[1*], Simhachalam Gurugubelli[2], Sai Kiran Attluri[3], Swetha Yadav Musty[4]

[1]Department of Internal Medicine, Piedmont Macon Hospital, Macon Georgia, USA

[2]Clinical Assistant Professor IU School of Medicine, Fortwayne, Indiana, USA

[3]MBBS AIIMS Mangalagiri, India

[4]Department of Internal Medicine, Piedmont Macon Hospital, Macon Georgia, USA

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***Corresponding author:** Bushra Firdous Shaik, Department of Internal Medicine, Piedmont Macon Hospital, Macon Georgia, USA

EPIDEMIOLOGY

Amyloidosis is a systemic disease characterized by the abnormal deposition of amyloid proteins in various tissues and organs, leading to disrupted organ function. Amyloids are misfolded proteins that aggregate into fibrils, which accumulate in extracellular spaces and tissues. With the most frequent type of amyloidosis being AL amyloidosis in the United States and AA amyloidosis in developing countries,[1] a relatively rare form (ALECT2) protein amyloidosis was discovered by Benson et al.[2] Based on the case reports published, data shows the disease appears to be more prevalent in regions such as Latin America, especially in Mexico.[3] There are cases reported from Northern India.[4] New studies show (ALECT2) protein amyloidosis is considered the third most common amyloidosis involving the kidneys in the United States, accounting for 2.5%-2.7% of renal amyloidosis cases. Worldwide, ALECT2 was found to be the second most common form of renal amyloidosis among Egyptians and was also reported among Pakistani, Sudanese, and Chinese populations.[5,6] In North America, approximately 90% of the reported cases of ALECT2 amyloidosis occur in older Hispanic adults of Mexican origin.[7] Studies show that ALECT2 amyloidosis is more commonly diagnosed in older individuals, especially those with renal transplants.[8] Although renal involvement is the most frequently reported, a case with hepatic involvement is reported from hispanic origin.[9]

PATHOGENESIS

ALECT2 is a 16-kDa protein produced by the liver and acts as a chemotactic factor to neutrophils and stimulates the growth of chondrocytes and osteoblasts. Benson et al. discovered ALECT2 amyloid in a nephrectomy specimen done for renal cell carcinoma. It was originally isolated and characterized from culture media of PHA-activated human T-cell leukemia cells in the process of identifying chemotactic factors important in the pathophysiology of neoplasia that happened to be amyloidogenic.[10] The human LECT2 gene has been localized to chromosome 5 (5q31.1-q32) and consists of four exons and three introns.[11] Though the in vivo role of it is unclear, in vitro studies show the limited expression of the gene in hepatocellular carcinoma. Overexpression of the gene shows inhibition of tumor cells and is believed to have a role as a tumor suppressor

gene against hepatocellular carcinoma (HCC). Additionally, LECT2 was shown to have a protective role in mouse models against bacterial sepsis, and increased expression following the infection with staphylococcus aureus and Aeromonas, suggests it may be implicated in certain inflammatory states, and this trigger could be a possibility for increased expression and amyloidogenesis.[12,13]

Larsen, et al. confirmed that there is a genetic polymorphism at nucleotide 172 in exon 3, and the replacement of isoleucine (A allele) with valine (G allele) at position 40 altering the structure could be responsible for amyloidogenic properties of LECT2. Patients with homozygous G allele are predisposed to LECT2 amyloidosis. [14]

CLINICAL FEATURES

The majority of cases reported show renal involvement. Some case reports provide extra renal involvement of ALECT2 amyloidosis. Studies show most patients are elderly and the initial presentation is with hypertension/ mild to moderate renal insufficiency with variable proteinuria. There are no known biomarkers for ALECT2 amyloidosis, and the only means to diagnose it is via biopsy or other tissue examination.[15] As the initial presentation does not warrant biopsy, the disease remains underdiagnosed. ALECT2 as the 3rd most common cause of renal amyloidosis[8] and is preferentially deposited in the interstitium of the renal cortex with milder involvement of the glomeruli and arterial walls, and it can also be deposited in the medulla.[3,7,15] In contrast to AL and AA amyloidosis, LECT2 amyloidosis is a relatively benign disease associated with a slow GFR decline and minimal proteinuria which could be explained by its deposition pattern.[2,3,7]

While many studies suggest LECT2 amyloidosis is restricted to kidneys, recent case reports show involvement of heart and spleen along with kidney, and deposition of amyloid protein in myocardial vessel walls including venules, arterioles, and capillaries.[3,16] Cardiac amyloidosis is most commonly caused by AL amyloidosis with transthyretin amyloidosis being the second most common cause.[17] Cardiac manifestations of amyloidosis in general include arrhythmias, conduction abnormalities or heart failure.

ALECT2 amyloidosis is the second most common cause of hepatic amyloidosis, presented with portal hypertension eventually leading to cirrhosis,[8,9] or it could be asymptomatic presentation incidentally discovered during evaluations for conditions unrelated to the liver or was associated with other causes of liver disease such as chronic viral hepatitis, suggesting that ALECT2 liver involvement might not be as clinically evident as that seen in kidney ALECT2. The median age of presentation is 60 years and are usually of Hispanic ethnicity.[15]

DIAGNOSTIC APPROACH

Similar to all amyloidosis, ACLET2 amyloidosis is a histological diagnosis done with biopsy. Light microscopy with an H&E stain typically shows an amorphous extracellular substance, and staining with Congo red reveals apple-green birefringence under polarized light.[18] Histologically, amyloid deposition usually occurs more in glomerulus and less in interstitium, which leads to proteinuria and hypertension. In contrary to other amyloidosis, ACLET2 deposition occurs more in interstitial space with strong congophilia.[7,19] ALECT2 primarily deposits in cortical interstitium compared to Apo AI amyloidosis and Apo AIV amyloidosis, which

mainly affect the medullary interstitium.[3,7] This lack of glomerular involvement is associated with minimal proteinuria and slow GFR decline. Using commercially available antibodies against LECT2, amyloid typing can be done with immunohistochemistry (IHC); however, its sensitivity is debatable due to antibodies recognizing only the wild-type protein.[20,21] Laser microdissection combined with mass spectrometry (LMD/MS) is commonly used for typing ALECT2 amyloid protein for its advantages over conventional methods. The avoidance of use of antibody and identification of false positives and negatives makes it preferable over IHC. But due to its limited availability, IHC is preferred first to rule out other forms of amyloidosis. Additionally, if the deposition of amyloid is more in cortical interstitium with strong congophilia, LECT2 amyloidosis should be suspected.

TREATMENT CONSIDERATIONS

Due to limited cases reported, there are no specific protocols developed to treat ALECT2 amyloidosis. Supportive therapy is to be provided based on the organ involved. Involvement of kidney being reported majorly, ALECT2 also involves other organs like heart and liver with few cases reported. With such scarce information, it is hard to make clinical guidelines for treatment of this entity, patients should be assessed based on individual needs (i.e. kidney transplantation, dialysis, etc.). Recurrence of ALECT2 is seen in one case. Compared with other amyloidosis, ALECT2 amyloidosis presumably has good prognosis, because of its less involvement of glomeruli and less chance of cardiac involvement.

Patient survival is superior to that seen in renal AL and AA, presumably because of the less chance of cardiac and glomeruli involvement. In a study, after a median follow-up of ~2 years, 30% of cases evolved into ESRD and some of them (n = 5) went on to receive kidney transplantation. Graft loss was not seen in any of these patients. However, recurrence of ALECT2 was registered in 1 case.[11]

CONCLUSION

ALECT2 amyloidosis, a rare but increasingly recognized form of systemic amyloidosis, is characterized by its predominant renal involvement and relatively benign clinical course compared to other types of amyloidosis. Despite its rarity, it has emerged as the third most common cause of renal amyloidosis in the United States and the second most common in specific populations such as Egyptians. Its unique pathogenesis, driven by genetic polymorphism and amyloidogenic properties of the LECT2 protein, primarily affects older individuals of Hispanic descent, particularly those of Mexican origin. The higher prevalence in this population suggests a potential genetic predisposition or environmental factors, though further studies are needed to clarify these risk factors and their role in disease development.

Diagnosis relies on histological techniques, with LMD/MS providing superior specificity. Clinicians in Mexico should consider ALECT2 amyloidosis in elderly patients presenting with chronic renal insufficiency and bland urine sediment, with or without proteinuria, to avoid underdiagnosis. Treatment remains supportive, emphasizing individualized care due to the absence of standardized protocols. More data is essential to develop targeted treatment protocols and identify specific risk factors. The relatively slow disease progression and limited organ involvement contribute to a favorable prognosis compared to AL or AA amyloidosis.

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