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A Little Review of LECT2-Associated Renal Amyloidosis (ALECT2): Is not a Rare Disease

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Abstract

We present a case of 69-year-old woman, who was referred to our hospital with the diagnosis of Chronic Kidney Disease (CKD) stage IV with unknown etiology. All the complementary tests carried out were normal; with no findings that suggested primary glomerular disease or systemic disease. The urine sediment had no alterations, with minimal proteinuria so at the beginning kidney biopsy was rejected. But after as the kidney function was getting worse and without a clear etiology of the disease; it was decided to carry out the renal biopsy; which showed against all the suspicions amyloid deposits. The pathology we describe is a new form of Amyloidosis, not previously registered in Spain, which differs clinically from the rest of Amyloidosis diseases studied so far. The bland urine sediment, and the slow progress of renal failure, result in an underdiagnosis, because of the kidney biopsy is not usually indicated, which is the only way to reach the diagnosis.

Keywords: Renal amylodiosis; Leukocyte cell-derived chemotaxin 2-associated amyloidosis; Kidney disease

Introduction

Amyloidosis is a heterogeneous and uncommon group of diseases characterized by abnormal accumulation and deposition of insoluble protein fibrils in the parenchyma of tissues, which result from a characteristic beta-pleated sheet conformation. Currently there are more than 30 proteins able to form amyloid in human [1]. This disease can be located or systemic and can affect any organ, being the kidney the most frequently involved organ in systemic amyloidosis classically, the two most common types of renal amyloidosis are primary amyloidosis or derived from plasma cell discrasia, mostly secondary to immunoglobulin light chains (AL) and rarely derived from fragments of Ig Heavy Chains (HA); and reactive AA amyloidosis (AA), which is associated with chronic inflammatory conditions.

There are several rare hereditary forms of amyloidosis, associated with an identifiable mutation in the protein responsible for amyloid, which are almost 10% of systemic amyloidosis. They are those derived from Fibrinogen A (Fib A), apolipoproteins AI, AII, AIV (AApoAI, AApoAII, AApoAIV), transthyretin (ATTR) gelsolin and Lysozyme (Alys), and all of which may also have renal involvement.

In addition to these classically known forms, a new form of amyloidosis has been described in the last years, the one derived from leukocyte chemotactic factor 2, called as ALECT2.

The LECT2 protein, isolated by Yamagoe in 1996, is a chemotaxin derived from the chemotactic factor of leukocytes 2. This is synthesized mainly in the liver, and also in cells of the vascular endothelium, smooth muscle, adipocytes and cells of the renal tubule. It is a multifunctional cytokine that participates in several functions: the chemotaxis of neutrophils, the inflammation and immunomodulation, the metabolism of glucose, the cell damage/repair process as well as it stimulates the growth of chondrocytes and osteoblasts. This emergent pathology has been described as one of the most frequent causes of renal amyloidosis in the United States [2], representing an important and underestimated cause of chronic kidney disease in patients from several ethnic groups around the world.

The etiopathogenesis of ALECT2 is still unknown. It has been described a genetic predisposition

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Table 1: Clinical characteristics of Amyloidosis derived from the chemotactic factor of leukocytes 2 adapted from Nasr et al.

Series	Larsen et al. [2]	Said et al. [4]
No. of patients	40	72
Affected organs demonstrated histologically	Kidney (100%), liver (2.5%), prostate (2.5%)	Kidney (100%), liver (1.3%), duodenum (1.3%)
Mean age at diagnosis (range), years	70.5 (52-86)	65.5 (43-88)
Man/woman	25/15	37/35
Hispanic ethnicity %	88	92
Average creatinine at diagnosis, mg/dl	2.8	3
Proteinuria %	33	79
Nephrotic range %	23	33
Medium urine proteinuria 24h g/day	0.6	1
Diabetes mellitus %	38	26
High blood pressure %	50	68
Monoclonal gammopathy	8	10
Average duration of follow-up, months	50	31
Progression to ESRD	6/21 (29%)	25/64 (39%)

and the existence of any mutation not known yet has not been ruled out. The clinical presentation is atypical to the rest of the Amyloidosis, with slowly progressive renal failure and lack of proteinuria. Histologically, it is characterized by amyloid deposition with predominance in the renal cortical interstitium, and scarce glomerular involvement. There is no specific treatment, and this pathology leads to terminal renal failure in 30% of patients. Survival is greater than in other types of amyloidosis due to the absence of cardiac involvement.

Case Presentation

We present the case of a 69-year-old woman from Nicaragua, who had been followed in another Hospital until December 2014, when she was referred to Hospital La Princesa, with the diagnosis of CKD stage IV with unknown etiology. Her medical history included high blood pressure well controlled with manidipine 20 mg and hypercholesterolemia in treatment with stations. She had had some urine infections, without microbiological documentation. She had not taken No Steroidal Anti-Inflammatory Drugs (NSAIDs) or other nephrotoxic drugs, and neither history of lithiasis. About her family medical history, her five brothers had hypercholesterolemia and hypertension, and her three children had not any cardiovascular risk factors. On physical examination she had not edema; and clinically, she had no asthenia or weakness, neither dysuria nor pathological urine characteristics.

Her analysis showed: Hemoglobin 11.2 g/dl; Creatinine 2.7 mg/dl; Urea 102 mg/dl; Glomerular Filtration (FG) according to CKD-EPI 18 mL/min/1.73 m^2. Albumin 4.6 g/dl and all the rest of determinations are without alterations.

Autoimmune profile showed weak positive Antinuclear Antibodies (ANAs) but negative by Immunofluorescence (IF). Anti Neutrophils Cytoplasm Antibodies (ANCAs) is a typical positive with PR3-ANCA and MPO-ANCA negatives. Normal complement pathway: Hepatitis B virus, hepatitis C virus, human immunodeficiency virus and syphilis were all negative; as well as all the tumor markers requested were also negative (alpha-fetoprotein, carcinoembryonic antigen, CA-125, CA 19-9). Urine sediment is without microhematuria and minimal proteinuria of 280 mg in 24-hour urine. As complementary tests, an abdominal ultrasound was performed in January 2015, showing a 10-cm-long left kidney and a 10.5-cm-long right kidney; both of us with adequate parenchymal thickness and good corticomedullary differentiation; without any lithiasis images or dilation of the excretory pathway.

Electrocardiogram is with sinus rhythm and without any alterations of repolarization or suggestive of ischemia and Transthoracic Echocardiogram is with left ventricle of normal dimensions with mild concentric hypertrophy. In February 2015, the kidney function got worse, with creatinine 3.2 mg/dL (FG of 15.32 ml/m). The urine sediment continued without any findings and the proteinuria was similar (200 mg/24 h) so, because of the absence of a clear etiology of renal failure, it was decided to perform a kidney biopsy on 02/23/2015. On examination with optical microscope, twenty-nine glomeruli were observed, of which only seven were conserved (glomerular sclerosis 75%). They showed discrete mesangial and occasionally membrane deposits, visible with hematoxylin-eosin, and negative staining with Masson and Methenamine silver. The most affection was in the cortical interstitium, with chronic inflammation and eosinophils. It highlighted the presence of an amorphous eosinophilic material, which stained with Congo Red and showed birefringence with polarized light, turning apple green, corresponding with amyloid.

This amyloid occupied the whole interstitium replacing the tubules and producing a marked atrophy-tubular. This deposit was also observed in the walls of some interstitial vessels and very focally in the glomeruli (Figure 1). In direct Immunofluorescence were used antisera Immunoglobulin (Ig) G, IgA, IgM, Complement (C) 3, C4, C1q and fibrinogen, without any deposits in the glomeruli, tubules or vessels. An immunohistochemical study was performed with amyloid A antibodies, kappa and lambda light chains, which were all negative.

The lack of expression of these antibodies and the peculiar distribution of amyloid deposits, with marked impairment of the interstitium and scarce glomerular involvement; added to the absence of nephrotic syndrome, as well as the Central American origin from the patient; made us conclude ALECT2 renal amyloidosis as the most likely diagnosis. We did not perform immunohistochemistry for LECT2 on the already Congo red stained slide; because this slide was an untreated glass one and it was needed a treated glass microscope

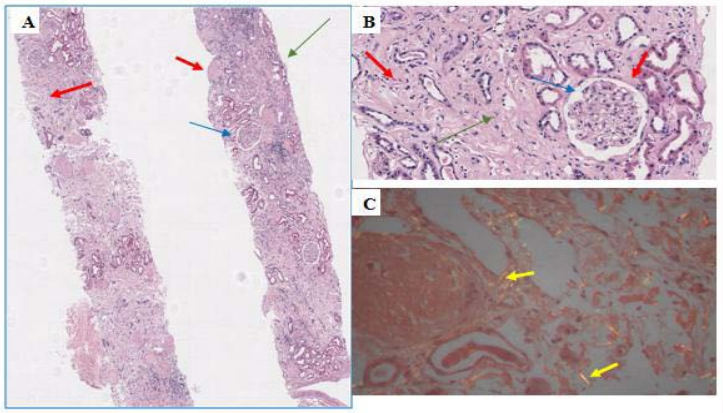

Figure 1: (A) Overview of two renal tissue cylinders that show hyaline amorphous deposits (red arrows) occupying the interstice, which are compatible with amyloid (hematoxylin-eosin, x20). **(B)** Demonstration that hyaline amorphous deposits (red arrows) at the glomerular level are markedly lower than in the interstitium (hematoxylin-eosin, x200). **(C)** Deposits of amyloid which shows green apple birefringence with polarized light (yellow arrows) (Congo Red, x40).
Note: 'The blue arrows point to the glomeruli, and the green ones indicate the interstice.

slide to perform immunohistochemistry. On the other hand, there was no more kidney tissue available, so, the sample could not be sent for analysis by Liquid Chromatography/Mass Spectrometer (LMD/MS).

With this suspected diagnosis, and because of the proposal of this disease as a possible familial amyloidosis with genetic predisposition, a genetic analysis was carried out with sequencing of the DNA of the patient, of her two children and of her grandchild. For knowing the genotype of the single nucleotide polymorphism rs31517 present in the LECT2 gene (NC_000005.10 on chromosome 5), a pair of oligonucleotides was designed to sequence a 646 BP DNA fragment, the sequence of which was: '-ATATGGTTATTAGCACCTGCGG-3' (sense) and 5'-CCCGATAGATATTTTTTTCTGATCC-3' (antisense). The patients' DNA was obtained from the blood using the Qiagen Midi Kit according to the manufacturer's instructions. Therefore, we conclude that the 4 subjects were homozygous for the nucleotide G in the SNP rs31517, which is characteristic of this disease and confirmed the suspicion of it.

Discussion

We describe a case of a little-known variety of amyloidosis, called ALECT2 or Amyloidosis derived from leukocyte chemotactic factor 2 it was discovered in 2008 by Benson et al. [3], but there was no knowledge of its importance until 2013 when Said et al. [4] described it as the third most frequent cause of Renal Amyloidosis (RA) in the United States. Later, in 2014, Larsen et al. [2] presented the largest series of cases of ALECT, recording it as the second cause of RA in the US, and the most frequent cause in the southwest (New Mexico, Arizona and Texas), with a clear predominance in patients of Hispanic origin (88%).

Thus, initially it was thought that it could mainly affect Hispanics in the US, until Larsen et al. [5] collected in 2016 the first series of cases which detailed the subtypes of RA among the Egyptian population, being amyloidosis ALECT2 the second most common type, representing almost a third of the cases of RA.

This has been done that is likely important, although little recognized, cause of end stage renal disease in other ethnic groups around the world. ALECT2 is the only one among amyloidosis in that the underlying etiology is currently unknown, although there are several hypotheses collected in the literature.

It is known that the LECT2 protein may be over expressed in liver diseases, from hepatocellular carcinoma or hepatitis, to fatty liver; but this does not explain the disease. Benson and Murphy describe it as a result of a genetic defect that interferes with the catabolic pathway or the LECT2 transport, with an increase in the local tissue concentration of LECT2, which would lead to the formation of amyloid fibrils.

However, patients with low plasma concentrations of LECT2 have been described, so that, high serum levels would not explain the etiology. On the other hand, it has been presented as a family Amyloidosis, because an ethnic predominance and the evidence of family participation are gathered in all the series, which presupposes a genetic etiology. Nevertheless, no mutations have been found in the LECT2 gene until now.

All patients have been homozygous for nucleotide G in a non-synonymous SNP at position 172 (rs31517 SNP). This polymorphism involves a change of the amino acid isoleucine by valine in the LECT2 protein, which produces a decrease in its stability, leading to a greater amyloidogenic propensity. This polymorphism is more frequent in Mexican ancestry, which is why it has been related to the origin and not to the pathogenesis of the disease, assuming a genetic predisposition, and considering it a necessary but not necessary condition to cause the disease. Currently, the existence of some unknown genetic mutation or the presence of environmental factors is not ruled out.

ALECT2 has a predominant renal involvement as the rest of the systemic amyloidosis, but with an atypical presentation. Mean age and the rate of creatinine at diagnosis were higher in all series published about ALECT 2 than the rest of Amyloidosis, with 70.4 years and 2.8 mg/dl respectively. This suggests that we are facing a slow process which begins at an early age with stable kidney function until late ages. Another characteristic feature is the bland urinary sediment, with infrequent microhematuria and the absence of significant proteinuria, lacking altogether in a third of the patients, and up to 40% of them with less than 200 mg/day.

Complete nephrotic syndrome is rare, unless there is a concurrent glomerulopathy. Among these, the most frequent are Diabetic Nephropathy (DN) (21%), nephropathy IgA (8%) and Membranous Glomerulonephritis (MGN) (5%).

In 2015, Nasr et al. a review of the current status of ALECT2 amyloidosis, summarizing the clinical findings of the two most extensive series reported (Table 1), describing a frequency of Diabetes Mellitus (DM) of 26% and 38%, and a High Blood Pressure (HBP) of 68% and 50%, in the series of Larsen et al. [2] and Said et al. [4] respectively. Regarding monoclonal gammopathy of uncertain significance, a frequency of 8% to 10% has been described, being fundamental not to confuse the diagnosis in these cases with primary AL amyloidosis.

Currently, there are no biomarkers known for this disease, being the tissue biopsy the only pathway for the diagnosis. Deposits have been described at multiple organs, such as spleen, liver, prostate and pancreas, however, they have not collected in skin or adipose tissue, so that less invasive procedures such as fat or skin biopsy do not seem useful. Therefore, an invasive procedure such as a renal biopsy which demonstrates the deposition of amyloid is necessary. There is no evidence of cardiac level deposits, assuming this as a significant difference from other types of amyloidosis.

Histologically the amyloid ALECT2 is characteristically congophilic, without describing significant differences with the rest of amyloid substances. It shows green apple birefringence with polarized light, and is negative for PAS, Masson's trichrome and silver methysteine staining. All the cases show deposition of amyloid which predominate in the renal cortical interstitium and with very scarce affectation in the medullary interstitium. In fact, in cases in which the deposits are restricted to the interstitium, amyloid could be missed histologically unless Congo red staining is routinely performed on all kidney biopsies.

The majority also show glomerular and arteriolar involvement, but very mildly. This contrasts with the typical glomerular involvement described in AA and AL/AH/AHL; as well as with morphological patterns with interstitial but predominantly medular involvement such as AApoAI/III/IV. The diagnosis by immunofluorescence is not always possible, since the antibodies used in the usual practice are directed against epitopes of the constant domains of Igs (IgG, IgA, IgM), lambda, kappa, C, fibrinogen, which may have been deleted. The typing of amyloid by immunohistochemistry, carried out with commercial preparations of specific monoclonal antibodies against the fibrillar proteins of amyloid, has been very sensitive, but could be little specific due to contamination with serum proteins that interact with amyloid and/or the humoral process reaction against fibrils of amyloid. That is why it has developed another technique with greater specificity, the liquid chromatography by laser/mass spectrometry (LMD/MS), which allows a single test to determine the amyloid precursor protein, giving the accurate diagnosis of the disease regarding treatment, currently, there is no effective therapy. It is important to differentiate it from other types of amyloidosis to avoid aggressive therapies with chemotherapeutic agents.

Kidney transplant has given good results in the short term, but the disease may recur in the renal allograft. The majority of patients suffer a slow deterioration of renal function, with an average drop in eGFR of 0.5 ml/min/1.73 m^2 per month. The renal survival is variable (median of 62 months), reaching End-Stage Renal Disease (ESRD) around 30% of patients. The survival is greater than in other types of amyloidosis due to the absence of cardiac involvement.

Conclusion

The bland urine sediment, the absence of findings in the study of autoimmunity and the slowly progressive course of the disease, meant that the patient was diagnosed prematurely over many years of CKD of unknown etiology; because of this disease is not clinically suspected, without considering the need to perform a renal biopsy initially. If this pathology had been known and the patient's ethnicity had been taken into account, it could have been suspected and diagnosed. ALECT2 is an emerging disease that is beginning to be recognized as an important cause of end stage renal disease in patients of his panic race. So, we consider that it is important to know about this pathology, and include it in the differential diagnosis of renal failure in our usual practice, given the high prevalence described in recent years.

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