A case report of hereditary apolipoprotein A-I amyloidosis associated with a novel APOA1 mutation and variable phenotype

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Abstract

Apolipoprotein A-I (apoA-I) amyloidosis is a non-AL, non-AA, and non-transthyretin type of amyloidosis associated with mutations in the APOA1 gene inherited in an autosomal dominant fashion. It is a form of systemic amyloidosis, but at presentation, can also mimic localized amyloidosis. The renal presentation generally involves interstitial and medullary deposition of apo A-I amyloid protein. We describe the identification of apo A-I amyloidosis by mass spectrometry in a 52-year old male, with no family history of amyloidosis, presenting with nephrotic syndrome and associated with heterozygosity for a novel APOA1 mutation (c.220T>A) which encodes the known amyloidogenic Trp50Arg variant. Renal amyloid deposits in this case were confined to the glomeruli alone, and the patient developed progressive renal impairment. One year after diagnosis, the patient had a successful kidney transplant from an unrelated donor. Pathogenic mutation in the APOA1 gene are generally associated with symptoms of amyloidosis. In this family however, genotyping of family members identified several unaffected carriers suggesting a variable disease penetrance, which has not been described before in this form of amyloidosis and has implications when counselling those with APOA1 mutations.
Introduction:

Amyloidosis is characterized by extracellular deposition of insoluble protein and peptides. Accumulation of amyloid in tissues, as well as oligomers of amyloid protein may cause organ damage, and if affecting the kidney, is often associated with progression to end stage renal disease. [Bergesio F, et al. 2008]


Mutations in the APOA1 gene are associated with autosomal dominant inherited amyloidosis [Van Allen MW, Frohlich JA, Davis JR, 1969]. To date, 20 different amyloidogenic mutations in APOA1 are listed in the Human Genome Database (HGMD: http://www.hgmd.cf.ac.uk/ac/index.php; accessed on June 2015). The majority of these are missense/nonsense mutations but small deletions/insertions have also been reported. The APOA1 gene mutations are associated with systemic amyloidosis, but can initially present as localized disease, particularly in the larynx and skin. Multiple organs including liver, kidneys, peripheral nerves, gastrointestinal tract, testes, spleen, heart, larynx, and skin may be involved. The clinical presentation varies from severe and progressive cardiac failure at the age of 20 and death in the late 4th decade, to late onset disease presenting in the 5th decade with gradually progressing renal failure. Renal involvement is common and most often characterized by amyloid deposition in the medullary interstitium and/or vasculature. In most cases of apoAI amyloidosis caused by APOA1 mutations,
there is a prior family history of similar disease (Table I) and so far, unaffected mutation carriers have not been described. [Erikson M et al, 2000]

**Results:**

A 52-year old Danish male with no family history of renal disease presented with hypertension, renal insufficiency, and nephrotic syndrome. At presentation, he had an eGFR of 36 ml/min/1.73m² and proteinuria in the range of ~7 g/24 h. A kidney biopsy revealed amyloid with extensive glomerular involvement (Figure 1). Immunostaining for serum amyloid A protein (SAA), kappa and lambda immunoglobulin light chains and transthyretin were all negative. A bone marrow aspirate and trephine biopsy were normal without clonal plasma cells or amyloid. Nerve conduction studies were normal and cardiac investigations, including echocardiography and cardiac biomarkers did not suggest cardiac infiltration by amyloid. Proteomic analysis of microdissected amyloid deposits from a kidney biopsy revealed large amounts of apoAI, which scored as number one, in conjunction with the amyloid ‘signature’ proteins serum amyloid P component and apolipoprotein E (figure 1D). Simultaneously, specific staining of glomeruli with antibodies against apoAI (figure 1B) also confirmed the presence of apoAI protein. Subsequent sequencing of APOA1 revealed heterozygosity for a mutation encoding the Trp50Arg variant, c.220T>A (cDNA reference sequence NM_000039.1). No mutations in other amyloid genes were identified. Except for paresthesia, there were no symptoms of extra-renal involvement by amyloid. Serum amyloid P component (SAP) scintigraphy revealed a large total body amyloid load with deposits in the liver, spleen, and kidneys (figure 1C). Despite treatment, including an angiotensin II receptor blocker and a statin, significant albuminuria persisted and kidney function declined to end-stage kidney disease within 10 months of diagnosis. Genetic analysis of the patient’s family identified the mother, two older brothers, and a
younger sister as mutation carriers but with no symptoms or signs of amyloidosis. The proband received a successful unrelated kidney transplant approximately 6 months later.

**Discussion:**

ApoA1 amyloidosis in this case was suggested by immunohistochemistry and confirmed by mass spectrometry [Sethi S. et al. 2013] and genetic analysis. An extensive work up showed no signs of monoclonal disease or inflammatory disease, supporting the pathogenicity of the glomerular apoA1 amyloid deposits presenting with nephrotic syndrome and leading to end stage renal failure. In general, renal involvement in apoA1 amyloidosis is believed to be medullary/interstitial rather than glomerular. In this case, however, the amyloid deposits were identified only in the glomeruli reported only in three other cases. (Table I)

A single case of an identical amino acid substitution due to a different, single nucleotide exchange (APOA1 c.220T>C) has previously been reported in a patient with a family history of amyloidosis. [Booth DR, et al. 1995]. The patient presented with symptoms of amyloidosis at age 35 years and had widespread organ involvement, including liver, spleen, and gastrointestinal tract. Renal involvement was noted in a kidney biopsy; however, kidney function only slowly declined leading to a kidney transplantation 10 years after presentation. In the current case, a culprit APOA1 mutation was identified in several family members with no signs or symptoms of amyloidosis, including the patient's mother at 80-years of age. Thus, the mutation and resulting amino acid substitution is associated with interfamilial and intrafamilial variability in disease penetrance. It is not known whether this may be due to variable expression of the variant. The recognition of this variation in disease penetrance is important for the counselling of clinically unaffected family members with a similar genotype.
In conclusion, the current case demonstrates the successful identification of apoAI amyloidosis by proteomic analysis of amyloid deposits associated with a novel APOAI mutation encoding a previously reported pathogenic apoAI variant. Genotyping of family members identified several unaffected older carriers indicating variable penetrance. The patient presented with nephrotic syndrome, which is unusual in this form of amyloidosis, and the renal biopsy showed isolated glomerular amyloid deposits that may mimic other types of amyloidosis.

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