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LETTER TO THE EDITOR

Hereditary systemic amyloidosis caused by K19T apolipoprotein C-II variant

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In 2017, Nasr and colleagues identified apolipoprotein C-II as the precursor protein of renal amyloid deposits in a 61-year-old woman with nephrotic syndrome and renal impairment using mass spectrometry (MS) [1]. Through DNA sequencing, they identified a heterozygous c.206A→T exon 3 mutation in the *APOC2* gene resulting in a glutamate to valine substitution at codon 69 (E69V mutation). In 2018, p.Lys41Thr apolipoprotein C-II variant was determined by the same investigators in renal amyloid deposits of 5 patients [2]. This newly recognized form of hereditary amyloidosis is probably underdiagnosed and an effort to collect data is important in order to describe clinical characteristics and outcomes. In this paper, we present a case of systemic amyloidosis due to p.Lys41Thr apolipoprotein C-II variant.

An 80-year-old Greek man presented with weight loss, deterioration of renal function (serum creatinine 6.7 mg/dl), and nephrotic syndrome (24-h urinary protein 4.04 g). He had a 15-year history of hypertension and chronic kidney disease (baseline creatinine 2.5-3 mg/dl). There was no family history of renal disease. He had two sons (41 and 44 years-old) with normal renal function. Blood tests showed normal liver function, cholesterol, triglycerides, HDL, and LDL levels. Renal ultrasonography showed reduced cortical thickness and multiple cysts consistent with chronic kidney disease. In view of the ultrasound findings, a renal biopsy was considered unsuitable. A biopsy specimen of abdominal fat stained with Congo red was positive for amyloid. Serum and urine protein electrophoresis with immunofixation were negative, and the serum free-light-chain ratio was 1.823. Bone marrow biopsy showed amyloid deposits in the periosteal vessels with no evidence of clonal plasma cells.

An attempt to type the amyloid by immunohistochemistry was unsuccessful. The paraffin blocks were subsequently sent for direct amyloid typing in the National Amyloidosis Centre. Liquid chromatography–tandem MS showed that the subcutaneous fat and periosteal deposits had a high content of apolipoprotein C-II; no other amyloid precursor protein was detected. Genomic

DNA was extracted from peripheral-blood cells and targeted sequencing of *APOC2* revealed a heterozygous mutation (c.122A→C) in exon 2, which causes the substitution of threonine for lysine at position 19 of mature apolipoprotein C-II (K19T), which corresponds to p.K41T mutation. The same heterozygous mutation was detected in his younger son. The patient's renal function worsened and he is currently receiving regular dialysis.

Apolipoprotein C-II is a co-factor of the enzyme lipoprotein lipase which is responsible for the removal of chylomicrons from circulation. When its activity is depressed, marked chylomicrominemia and hypertriglyceridemia develop [3]. The normal triglyceride levels in our patient may suggest that K19T variant apolipoprotein C-II has no major impact on lipoprotein metabolism.

The diagnosis of hereditary apolipoprotein C-II amyloidosis at an older age is consistent with a slowly progressive course. The history of chronic renal disease for several years before the diagnosis, the slow deterioration of renal function, and the lack of any renal-function abnormality in his son support the hypothesis that this is a disease with a late onset of symptoms. The details from this case indicate that K19T apolipoprotein C-II amyloidosis (AApoCII) is inherited as an autosomal dominant disorder.

In conclusion, the findings of this case expand our knowledge of *APOC2* K19T mutation, show that variant apolipoprotein C-II may deposit in soft tissue and therefore AApoCII can be diagnosed by subcutaneous fat biopsy, and support the suggestion that AApoCII is associated with older age and kidney involvement. This case also highlights that physicians should maintain a high index of suspicion for hereditary amyloidosis in adults presenting with the nephrotic syndrome, even in older age-groups. Hereditary systemic apolipoprotein C-II amyloidosis should be included in the differential diagnosis of these patients.

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