Mixed leukocyte cell-derived chemotaxin 2 and amyloid A renal amyloidosis in a Kazakh-German patient

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Abstract

Leukocyte cell-derived chemotaxin 2 (LECT2)-related amyloidosis (ALECT2) constitutes a subtype of systemic amyloidosis affecting the kidney. This is the first case describing mixed ALECT2 and Amyloid A renal amyloidosis in a Kazakh-German patient. Genetic analysis shows a polymorphism in the LECT2 gene and a homozygous mutation in the SAA1 gene. Notably, our patient has a body mass index of 61 kg/m² and a pathological glucose tolerance test. ALECT2 was found in certain ethnic groups with a high incidence of diabetes. In our case, morbid obesity may have played a significant role in clinical manifestation of ALECT2 amyloidosis.

Key words: amyloidosis, gene expression, immunohistochemistry, obesity, renal biopsy

Background

Amyloidosis caused by leukocyte cell-derived chemotaxin 2 (LECT2) has only recently been recognized [1, 2] and was found particularly in patients of specific ethnic groups. No case of mixed Amyloid A (AA) and LECT2 amyloidosis has been described so far.

Case report

A 53-year-old Kazakh lady with German predecessors presented to her community doctor and was found to have worsening renal function. At this time, she had no symptoms such as raised blood pressure, haematuria, flank pain or peripheral oedema. Incidentally, she noted having a loss of gustatory perception over time.

She had been diagnosed with a pathological glucose tolerance test and arterial hypertension 3 years earlier. She is morbidly obese with a body mass index (BMI) of 61 kg/m². Her past medical history includes tuberculosis in 1984, cholecystolithiasis and hypothyroidism. Her medication includes an angiotensin-converting enzyme inhibitor, a betablocker and thyroxine.

Due to worsening renal function (estimated glomerular filtration rate MDRD 36.5 mL/min), proteinuria 113 mg/mmol
creatinine (1000 mg/g creatinine) and evidence of dysmorphic erythrocytes in the urine sediment (11 per high power field), a renal biopsy was performed and showed glomerular, tubulointerstitial and vascular AA deposits as well as immunoglobulin A (IgA)-associated mesangiproliferative glomerulonephritis Oxford Classification M0 E1 S1 T2.

Serum amyloid A level was raised with 81 mg/L (81 µg/mL). C-reactive protein (CRP) level was 60 mg/L (6.3 mg/dL). Immunological screening was unremarkable, including negative antineutrophil cytoplasmic antibodies (ANCA), rheumatic factor, anti-cyclic citrullinated peptide (anti-CCP) antibodies, myositis panel antibodies, anti-extractable nuclear antigen antibodies (ENA) and normal complement factors. Antinuclear antibodies (ANA) titer was slightly raised with 1:160. Total serum immunoglobulin E level was elevated at 440 IE/mL. Serum IgA level and IgG subclass differentiation, including IgG4 levels, were normal. Testing for HLA-B27 was negative. A genetic predisposition for autoinflammatory syndromes such as cryopyrin-associated autoinflammatory syndrome (CAPS) and tumour necrosis factor-associated periodic syndrome (TRAPS) was ruled out.

However, interferon-gamma-release assay was positive, indicating either previous or acute infection with mycobacterium tuberculosis. Bronchoscopy, gastric fluid aspiration and bone marrow biopsy were performed and showed no evidence of mycobacterium tuberculosis infection. During the clinical course, interferon-gamma-release assay became negative.

Genetic investigations revealed a homozygous presence of the SAA1alpha/SAA1.1/Val52(GTC)/Ala57(GCG) allele, consistent with a genetic predisposition for AA amyloidosis. Sequencing analysis of all four protein coding exons of the LECT2 gene showed heterozygous presence of a G polymorphism at cDNA position 172 (c.172A > G) leading to the replacement of isoleucine by valine (p.Ile58Val/I58V; legacy name I40V). No other mutation was detected in the LECT2 gene. Other genetic causes for amyloidosis were ruled out.

Therefore, biopsy specimens from the kidney were further analysed. Immunostaining was carried out using antibodies as described in detail elsewhere [3]. Renal amyloid deposits showed strong and even immunostaining with antibodies directed against amyloid P-component and AA amyloid. In addition, some deposits also showed strong immunostaining for LECT2, while the surrounding tissue was entirely immunonegative for LECT2 (Figure 1).

Due to raised inflammatory markers, treatment with colchicine at a dose of 0.5 mg twice daily was started. After 6 weeks, serum amyloid A level was normalized with 6.2 mg/L (6.2 µg/mL) and CRP level was 15 mg/L (1.5 mg/dL). Therapy was well tolerated. Gustatory taste had recovered. Exercise tolerance and general well-being improved.

Discussion

Amyloidosis describes a group of diseases with different aetiologies, characterized by the extracellular deposition of peptides and proteins oriented in a β-sheet structure leading to insoluble fibrillar aggregates. AA amyloidosis is usually caused by chronic inflammation, for example autoimmune disease, hereditary fever syndromes or chronic infections, with or without a variation in the SAA1/2 gene.

This is the first report of mixed AA- and ALECT2-amyloidosis with a genetic variation in the SAA gene and a heterozygous polymorphism in the LECT2 gene.

Fig. 1. Amyloid in a kidney biopsy. On an H&E-stained section (A), a homogeneous eosinophilic material was found in the glomerula and tubulo-interstitially. Congo red stains the deposits and shows yellow–green–orange birefringence (B). The amyloid deposits immunoreact with an antibody directed against AA amyloid (C) and Lect2 (D). Original magnifications 400-fold.
ALECT2 amyloidosis has been predominantly found in Mexican American patients [4] and also in other patients of different ethnicities. Genetic studies found that all patients with ALECT2 had a homozygous G allele polymorphism in the LECT2 gene [4]. It has been suggested that a second factor, either genetic or environmental, is necessary to cause clinical manifestation of ALECT2 [4].

It was shown that 38% of patients with ALECT2 amyloidosis suffer from diabetes mellitus [4]. Possibly, this is an underestimation, as some of the patients may not have been diagnosed with diabetes at the time of biopsy, particularly if it was a post-mortem examination. To our knowledge, data on the prevalence of obesity in ALECT2 patients do not exist.

Mexican Americans are known to have a higher prevalence of diabetes mellitus than Caucasians [5]. Our patient has marked obesity and shows a pathological glucose tolerance test.

We present a case of mixed AA- and ALECT2-renal amyloidosis in a Kazakh-German lady with a polymorphism in the LECT2 and a variation in the SAA gene. This genetic susceptibility, together with marked obesity (BMI of 61 kg/m²), may have contributed to clinical manifestation of the disease.

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**Conflict of interest statement**

We have no conflict of interest to declare. The results presented in this paper have not been published previously in whole or part.

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